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WHAT'S INSIDE

The benefits of B cells

Multiple studies point to B cells' role in promoting anti-tumor immunity

BY MEL J. YEATES

HOUSTON—According to researchers at The University of Texas MD Anderson Cancer Center, the likelihood of a patient responding to immune checkpoint blockade may depend on B cells in the tumor, located within specialized immune cell clusters known as tertiary lymphoid structures (TLS). Recent studies published in *Nature* have concluded that enrichment of B cells in TLS was predictive of response to checkpoint blockade in patients with melanoma, renal cell carcinomas (RCC) and soft-tissue sarcomas.

The studies conclude that the presence of B cells and their location within TLS, which act as a lymph node within the tumor, is critical for response to checkpoint blockade. This suggests a dynamic interaction between several immune system components.

One MD Anderson-led study found that B-cell markers were the most differentially expressed genes in responders relative to non-responders, and B cells in the tumors of responders appeared to be more mature and specialized.

CREDIT: MD ANDERSON CANCER CENTER

"These findings open up a whole new area—that B cells are actually big drivers in cancer immunotherapy, specifically checkpoint blockade," says Dr. Jennifer Wargo of the MD Anderson Cancer Center about recent research published in *Nature*. "This could lead us to important biomarkers for therapy response as well as potentially new therapeutic options."

"Although the distinct mechanisms through which B cells contribute are incompletely understood, our data suggest that the same properties of memory B cells and plasma cells desirable for acquired immune responses may also be contributing to an effective T cell response after ICB [immune checkpoint blockade]," the article explains. "Importantly, these B cells are probably acting together with other key immune constituents of the TLS by altering T cell activation and function as well as through other mechanisms. Memory B cells may be acting as antigen-presenting cells, driving the expansion of both memory and naive tumour-associated T cell responses."

"These findings open up a whole new area—that B cells are actually big drivers in cancer immunotherapy, specifically checkpoint blockade," said corresponding author Dr. Jennifer Wargo, a professor of genomic medicine and surgical oncology. "This could lead us to important biomarkers for therapy response as well as potentially new therapeutic options."

The team analyzed samples from patients with advanced melanoma receiving neoadjuvant checkpoint inhibitors as part of a clinical

B CELLS CONTINUED ON PAGE 15

CREDIT: ABBVIE

Cosentyx has a bit of legacy for Skyrizi to overcome, having been approved by the FDA in January 2015 and holding a strong market share since then, but AbbVie (pictured here) and partner Boehringer Ingelheim hope that recent data in a head-to-head study could give Skyrizi a market edge.

A competitor for Cosentyx

AbbVie and Boehringer Ingelheim's Skyrizi showed superiority to Novartis' Cosentyx in Phase 3 trial of plaque psoriasis

BY KELSEY KAUSTINEN

NORTH CHICAGO, Ill.—Plaque psoriasis is an immune disease in which red, scaly patches appear on the skin, most commonly on the scalp, knees, elbows or lower back. According to the National Psoriasis Foundation, the exact cause of the disease is unknown, but "Scientists believe that at least 10 percent of people inherit one or more of the genes that could eventually lead to psoriasis. However, only 2 percent to 3 percent of the population develop

SKYRIZI CONTINUED ON PAGE 28

Finding mutations, matching treatments

Clinical trial indicates that blood test beats biopsies for breast cancer

BY ILENE SCHNEIDER

LONDON—Breast cancer, the most common cancer in the United Kingdom, shows up in 55,200 new cases per year. Women diagnosed later or relapsing after treatment have limited treatment options, and if the cancer is diagnosed at the latest stage, only one in four people (25 percent) will survive the disease for five years or more.

Some breast cancers with specific mutations, or genetic defects, can be targeted directly with new drugs undergoing testing in clinical trials. Since these defects are rare, it is critical to determine which patients could benefit most. Currently, these defects are identified by taking out a piece of the tumor via biopsy or during surgery, a slow, invasive process that may be inaccurate after treatment or when cancer spreads.

Cancer Research UK scientists have found that a blood test can help identify rare mutations in advanced breast cancer, potentially enabling patients to access effective treatments more quickly in the future. Their results were presented at the 2019 San Antonio Breast Cancer Symposium.

As part of the plasmaMATCH clinical trial—funded by Stand Up To Cancer, a joint

CREDIT: CANCER RESEARCH UK

Cancer Research UK scientists have found that a blood test can help identify rare mutations in advanced breast cancer, potentially enabling patients to access effective treatments more quickly in the future.

fundraising campaign from Cancer Research UK and a television station—the researchers were able to discover mutations in the DNA from the tumors, which shed cells into the bloodstream. Specific weaknesses in the breast cancer DNA could be targeted with drugs, suggesting that this blood test may be a better way to guide treatment than standard tissue biopsies that can be painful and take longer to analyze.

Researchers at The Institute of Cancer Research, London, and The Royal Marsden NHS Foundation Trust analyzed the blood

BLOOD CONTINUED ON PAGE 31

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Multiple sclerosis market to reach $32.9B in 2028

LONDON—The multiple sclerosis (MS) therapeutics market has entered "an exciting phase" by the reckoning of data and analytics company GlobalData, with an upsurge of available treatment options and several promising late-stage pipeline products offering diverse mechanisms of action (MOAs). The MS market is expected to grow in sales from $19.8 billion in 2018 to $32.9 billion in 2028. This represents a compound annual growth rate of 5.2 percent, and is said to be due to the launch of 11 new pipeline agents providing more options for patients and stimulating further competition.

Those new agents have a broad range of MOAs, including anti-CD20 antibodies, three second-generation S1P receptor modulators, an anti-LINGO-1 antibody, a tyrosine kinase inhibitor, a repulsive guidance molecule A (RGMA) inhibitor, and antioxidants.

According to GlobalData, the MS pipeline is strong and diverse, with a total of 49 products in all stages and phases of clinical development; of those, 24 are early-stage and 25 are in the late-stage pipeline. Progressive MS is a significant focus for product development, with seven of the late-stage products targeting this patient group as an initial indication. There is currently a distinct lack of disease-modifying therapies for patients with progressive MS subtypes, and these populations remain significantly underserved.

"The launch of Mayzent in March 2019 and the potential launch of two other receptor inhibitors—ozanimod and ponesimod—will increase competition in the MS market, and these new drugs will take patient share from the approved treatment—Novartis' Gilenya," said Alessio Brunello,

MS CONTINUED ON PAGE 4

Venture funding for AI in drug development and trials hits $5.2B

CRANFIELD, U.K.—According to data from Signify Research, the market for artificial intelligence (AI) technology in the drug development and clinical trials markets is maturing and entering a new phase.

However, while total funding in this industry segment has reached $5.2 billion, investments slowed down in 2019 and only four new companies were formed. Any new startups will have to prove themselves able to compete against well-funded first-generation vendors, notes Signify Research, and existing vendors are under pressure to demonstrate results.

Which applications use AI?

Nine out of 10 new drug candidates never make it through clinical trial and regulatory approval, so the pharmaceutical industry is very open to new ways that can make drug development more efficient. The focus of the Signify Research analysis was on applications that are directly involved in optimizing drug development by analyzing clinically relevant data to guide the discovery of new potential targets; applications that are directly involved in the creation and optimization of the molecular structure of potential drugs; and applications that help organize, optimize, run and recruit patients for clinical trials.

Information synthesis—To aggregate and synthesize information is fundamental to AI applications being used in both drug design and clinical trials. Platforms are typically delivering broad data analysis and predictive models based on machine learning and deep learning algorithms. This category captures vendors using AI to analyze clinical data and real-world evidence across different applications, which can then be used in clinical trials or drug design. Any integrated information synthesis functionalities in drug design or clinical trial applications are instead included in each of those categories.

Drug design—Compared to the other two product segments included in this investment analysis, startups developing AI for drug design are leading in terms of number of companies and total amount of funding so far, and several new drugs are currently going through clinical trials. AI is generally being applied to identify patterns hidden in large volumes of data or calculating the effect of small molecular iterations to optimize and predict efficacy and specificity. Within this field, the applications are often interrelated and include using AI to analyze clinical, scientific, patient and genomic data to get a better understanding of disease mechanisms, and using this to generate either novel drug candidates or to repurpose existing drugs for new diseases and therapeutic uses. Once potential targets have been identified, AI is also being used to accelerate the drug design process by performing *in-silico* experimentation and conformational analysis on drug molecules to gain insights into the behavior and physical properties of the molecule prior to *in-vitro* and *in-vivo* testing.

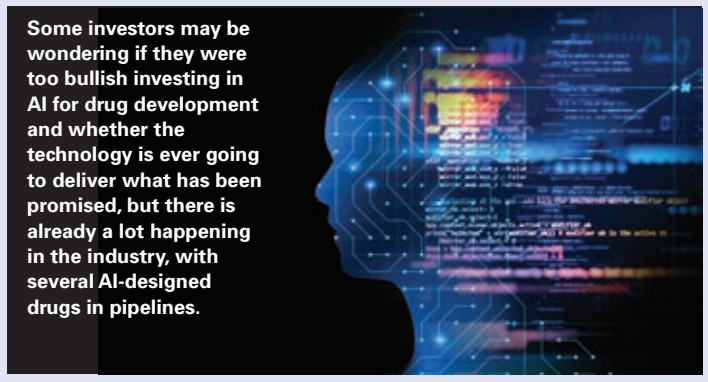
Clinical trials—This is an area with great potential for optimization, as only 12 percent of drug development programs ended in success in a 2000-2019 study on clinical trial failure rates. Inability to demonstrate efficacy or safety, flawed study design, participant drop-outs or unsuccessful recruitment all contributed to the low success rate of clinical trials. Vendors active in this field are therefore focusing use of AI around three main areas: natural language processing to enable analysis and decision making from structured and unstructured data from medical records, relevant guidelines, real-world data and other sources that could potentially enhance the quality and efficiency of clinical trials; clinical trial design and optimization pulling in information from comparable studies, clinical data and regulatory information to optimize eligibility criteria, cost, length and retention; and clinical trial recruitment using natural language processing to analyze doctors' notes and clinical data such as pathology reports and patient history in medical records to determine the pool of potential subjects, or help clinicians find relevant clinical trials and treatments for their patients by analyzing electronic medical records and genomic data for improved clinical trial matching.

Within these three product segments, 32 percent of funding has gone to companies focusing on information synthesis, 54 percent to companies focusing on drug design, and 14 percent to companies with a primary focus on clinical trials.

AI in drug development vs. AI in medical imaging

AI in drug development and clinical trials has seen tremendous initial investment. Compared to AI in medical imaging the total investment has been more than fourfold, even though the number of funded startups is equivalent (101 funded startups in medical imaging against 106 funded startups in drug development and clinical trials). With 231 deals in medical imaging and 303 deals in drug development, the average deal size in drug development is 3.5 times bigger than in medical imaging.

AI in medical imaging and AI in drug development are two very different markets with their own characteristics. While medical imaging is very well suited for the use of machine learning-based pattern recognition, adoption within healthcare providers is a notoriously slow process due to a lack of trust in AI amongst clinical staff, a value proposition which is difficult to prove, complex data integration due to siloed and proprietary imaging platforms,



Some investors may be wondering if they were too bullish investing in AI for drug development and whether the technology is ever going to deliver what has been promised, but there is already a lot happening in the industry, with several AI-designed drugs in pipelines.

not to mention the challenging and uncertain regulatory approval process.

Despite requiring more complex solutions, AI in drug development has seen much more interest from the investment community. As Big Pharma is struggling with profitability due to high R&D costs, low success rate for new drugs, difficulty in enrolling patients for clinical trials and pressure on companies from governments to cut prices on pharmaceuticals, the industry is searching for new ways to reduce the cost of drug development and regain profitability. Not working in a hospital care setting takes away some of the regulatory challenges and the complex go-to-market strategies. So, once the technologies have proven themselves ready for market with successful drug candidates and clinical trials, investors are expecting high returns through partnerships with the pharma industry.

AI in drug development—more than empty promises?

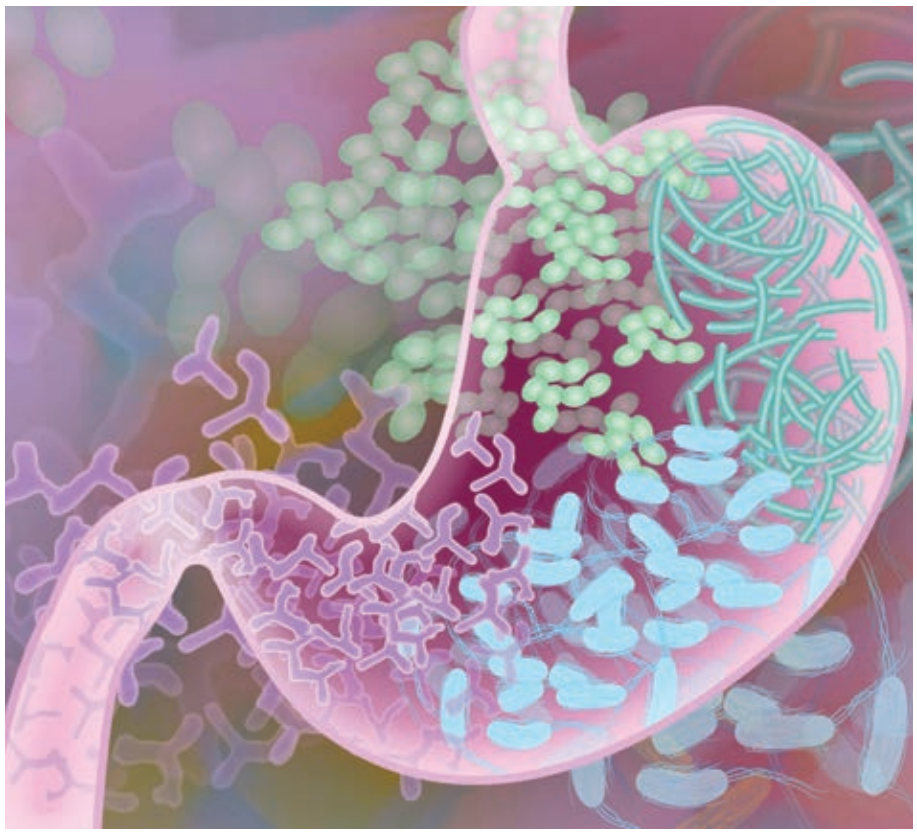
While the number of companies founded in year 2017 peaked at 28, only four new companies were formed in year 2019. In addition, total funding decreased by 23 percent from 2018 to 2019. Ambitions and expectations have been sky-high for AI use in this sector, but some investors may now start to wonder if they had been too bullish and if the technology is ever going to deliver what has been promised.

Even if AI would be able to assist with such a complex task as understanding the cause of disease, it would need access to vast amounts of data that is often not accessible or simply does not exist yet. So, as the market matures past the initial hype, investors—as well as potential new pharma partners—are waiting to see more evidence and proof of concept to demonstrate the functionality and value of these AI solutions.

However, there is already a lot happening in the industry, with several AI-designed drugs in the pipelines. Partnerships with big pharma vendors will be key to success for startups and will support turning proof of concept into potential milestone payments for new drug candidates, sometimes exceeding a billion dollars, as seen with the InSitro-Gilead partnership, Exscientia-Celgene partnership and Atomwise-Hansoh Pharma partnership.

And, in addition to revenue, as pharmaceutical companies often are sitting on years of digitized data from research and clinical trials, the pharma partnerships will provide access to a larger pool of data to train the algorithms and discover new valuable connections in disease and treatment mechanisms that wouldn't have been possible otherwise with traditional methods. ■

Adapted from a summary/article about the Signify Research data by Ulrik Kristensen of Signify Research.



CREDIT: DARRYL LEJA/NHGRI

HUMAN MICROBIOME MARKET IS PROLIFIC

LONDON—According to Roots Analysis, which recently announced the addition of "The Human Microbiome Market, 2019-2030" report to its list of offerings, the market in question is projected to be worth more than $4 billion by 2030, growing at an annualized rate of over 40 percent.

Over the years, extensive R&D efforts have established the basis for a wide range of microbiome-based therapeutic and diagnostic products, which may cause a paradigm shift in the way healthcare is delivered in the foreseeable future, according to Roots Analysis. It adds that the concept of microbiome-based therapeutics has generated significant enthusiasm within the medical science community, defining a new frontier in the field of medicine.

Some key findings of the report include:

▪ Around 260 therapy candidates are currently in different phases of development, and nearly 25 percent of pipeline drugs are in the clinical phase of development, while the rest are in the preclinical/discovery stage. Interestingly, most of these drugs target digestive and gastrointestinal disorders (20 percent), and this is followed by product candidates intended for treatment of oncological disorders (17 percent) and infectious diseases (13 percent).

▪ Over 30 microbiome diagnostic tests are currently available or under development. Around 30 percent of these tests have been commercialized, while the rest are under development.

▪ Fecal microbiota transplants are the only commercially available microbiome therapy. This therapeutic product is presently indicated for the treatment of recurrent *Clostridium difficile* infections. Further, non-industry players (such as University of Alberta, The Second Hospital of Nanjing Medical University, University of California and Chinese University of Hong Kong) are making notable contributions in this arena, having been involved in more than 200 clinical trials since August 2019.

▪ Approximately 51-percent growth in capital investments has been observed since 2015, with around 70-percent investment coming from Venture Capital investors. It is worth noting that more than 80 investors have supported the R&D programs initiated by startups focused on microbiome-related products. Well-funded startups have initiated product development programs, having invested significant time and effort to explore the applicability of microbiome therapeutics across various indications.

▪ Several large pharma players have microbiome-related initiatives. Leading pharmaceutical companies have actively partnered with smaller business entities to develop capabilities related to microbiome-based therapies and diagnostics.

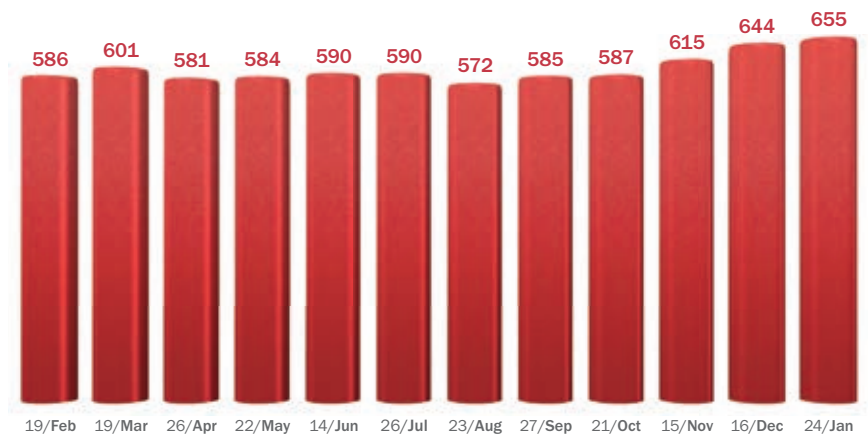
▪ Contract service providers have become an integral part of the microbiome supply chain. Presently, certain firms claim to offer a wide array of contract research and manufacturing services for microbiome therapeutics.

▪ North America and Europe are anticipated to capture over 85 percent of the market share by 2030. As late-stage products are commercialized, the microbiome therapeutics market is likely to grow at an annualized growth rate of over 30 percent during the next decade. In addition to North America and Europe, the market in China and the broader Asia Pacific region is also anticipated to grow at a relatively faster rate.

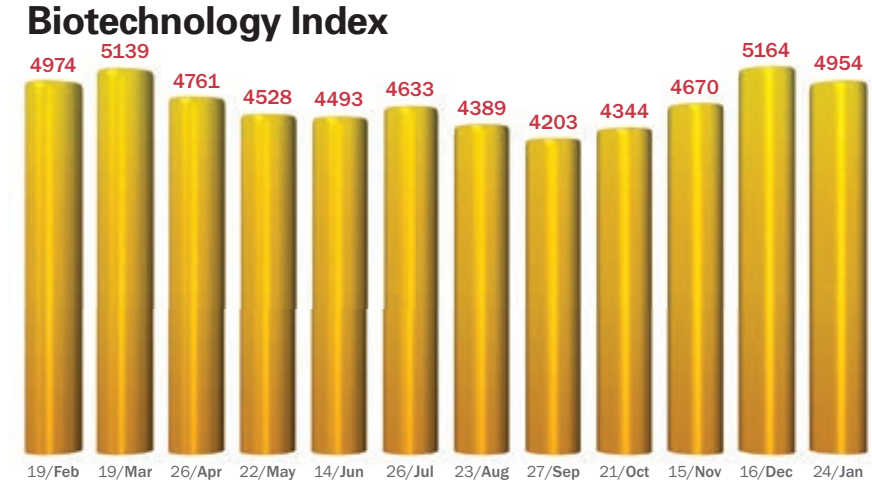
Despite having captured the interest of several venture capital firms and Big Pharma players, though, no microbiome-based therapeutic has been officially approved by an authorized medical product regulator. However, the current development pipeline of microbiome therapeutics has several promising candidates that are likely to result in commercial success stories soon, Roots Analysis maintains. ■

MARKET INDICES

Pharmaceutical Index



Biotechnology Index



SOURCE: NYSE ARCA

MS

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a senior pharma analyst at GlobalData. "Gilenya's market share would have been undermined by generic erosion following U.S. patent expiries in 2019, but Novartis gains temporary injunction from generic competition of the U.S. Gilenya patent, which means that the patent will now expire in December 2027; however, there could still be generic entry in 2022 based on other litigation."

The current MS market is highly competitive, with 14 available treatment options, most of which are immunomodulatory agents. The majority of approved treatments address the inflammatory and systemic origins of the disease, but few possess neuroprotective effects and, as such, have an insufficient impact on the underlying neurologic deterioration caused by MS. Two pipeline drugs—namely, opicinumab and elezanumab—could address this need, as they promote axonal regeneration and myelination.

Added Brunello: "Remyelination strategies could prove revolutionary for MS, as they address a key pathophysiological aspect of the disease that is thought to contribute to the accrual of permanent disability."

Two additional monoclonal antibodies, from Novartis (ofatumumab) and TG Therapeutics (ublituximab) are expected to launch in the forecast period, despite physicians being satisfied with Roche's/Genentech's Ocrevus (ocrelizumab). Key opinion leaders have explained that it is possible that there may be some advantages to ofatumumab, but nothing that would have a huge impact over the ocrelizumab market.

"The MS market is heading towards earlier and more aggressive therapies, with studies in the U.S. questioning whether people with MS who are recently diagnosed should already go on with one of the monoclonal antibody therapies."

Alessio Brunello, a senior pharma analyst at GlobalData

"The MS market is heading towards earlier and more aggressive therapies, with studies in the U.S. questioning whether people with MS who are recently diagnosed should already go on with one of the monoclonal antibody therapies," concluded Brunello. ■

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DISCOVERY

BRIEFS

Seeking success with SITESEEKER

CAMBRIDGE, U.K.—PhoreMost Limited and Boehringer Ingelheim have teamed up in a multi-project drug discovery collaboration under which PhoreMost will apply its SITESEEKER next-generation phenotypic screening platform to identify novel targets in disease-relevant pathways selected by Boehringer Ingelheim. Though specific financial details were not released, the agreement stipulates that PhoreMost will receive an upfront payment, research funding and downstream success-based milestone payments. Boehringer Ingelheim will validate and characterize any identified targets.

Dr. Chris Torrance, CEO of PhoreMost, said: "We are delighted that Boehringer Ingelheim has chosen to work with PhoreMost to enhance its drug discovery pipeline with attractive biological starting points. The collaboration is further recognition of the ability of PROTEINi and SITESEEKER to identify novel targets, and we look forward to working with the Boehringer Ingelheim team on these projects."

Machine learning for target discovery

NEW YORK—Insilico Medicine has found its latest partner in Pfizer Inc., as the companies announced a research collaboration in mid-January to leverage Insilico's Pandomics Discovery Platform to identify real-world evidence for potential therapeutic targets implicated in several diseases. Financial details were not disclosed. Insilico specializes in machine learning to generate "new molecular structures with the specified parameters, generation of synthetic biological data, target identification and prediction of clinical trials outcomes," the company says.

"We look forward to working with Insilico as Pfizer continues to explore new technologies that may be able to help us identify targets and biomarkers that could assist in our discovery programs, and potentially lead to breakthrough therapeutics for patients with unmet medical needs," noted Morten Sogaard, vice president, Target Sciences, Pfizer.

IN THIS SECTION

Proprietary platform

Lodo reinvents environmentally sourced, natural product drug discovery

BY ILENE SCHNEIDER

NEW YORK—Drugs originating from biological, rather than synthetic, sources now make up the majority of available medicines, yet they all stem from the relatively few microbes that are easily cultured.

Lodo Therapeutics, under the leadership of its new CEO—serial biotech executive Dr. Dale Pfost—uses next-generation sequencing (NGS), artificial intelligence and synthetic biology to find new compounds that are hidden in the huge volume of microbial DNA. Such microbial molecules have great therapeutic potential because they have helped microbial life to continue for vast periods of time.

Lodo is trying to acquire data on the molecules directly from microbial DNA without having to culture the microbes and evaluate their byproducts first, which both speeds up research and lowers costs. The company is using its direct-access technologies to find new antibiotics for use against tuberculosis and other diseases, and anticancer drugs as well.

CREDIT: LODO THERAPEUTICS

Lodo Therapeutics is using next-generation sequencing, artificial intelligence and synthetic biology to find new compounds that are hidden in microbial DNA.

Formed in 2016 by Accelerator Corporation, a leading life-sciences investment and management firm, Lodo seeks to develop novel therapeutics by applying its

LODO CONTINUED ON PAGE 8

"With this agreement, along with the advancement of the Acceleron-discovered assets sotatercept—in Phase 2 trials in pulmonary arterial hypertension—and ACE-1334, we underscore our growing commitment to the development of novel therapies for patients with pulmonary diseases of high unmet medical need," says Habib Dable, CEO of Acceleron Pharma.

PARTNERING FOR PULMONARY DISEASE

Rare disease-focused companies link up to identify, develop therapeutics

BY KELSEY KAUSTINEN

CAMBRIDGE, Mass.—Acceleron Pharma and Fulcrum Therapeutics have a collaboration and license agreement underway for the new year as they join forces to identify small molecules against a pulmonary disease target. Acceleron is focused on the discovery and development of therapeutics within the TGF-beta superfamily for the treatment of rare diseases, and Fulcrum shares that focus on orphan diseases, though its niche of choice is genetically defined rare diseases.

"This collaboration brings together Fulcrum's skill in identifying drug targets based on modulation of genetic pathways

PULMONARY CONTINUED ON PAGE 9

Can baldness be stopped?

Mount Sinai shares new information regarding the dermal sheath found around hair follicles

BY KRISTEN SMITH

NEW YORK—Following up on a hypothesis posited as far back as 1991, researchers at Mount Sinai have identified a specific mechanism within the hair growth cycle that results in hair loss. The resulting hope is that this mechanism can someday be pharmacologically controlled, thereby slowing or stopping hair loss.

"The hair-growth cycle is asynchronous. We don't know what kicks in the destructive phase, or what underlying 'clock' is at work."
Dr. Michael Rendl, associate director of the Black Family Stem Cell Institute

The dermal sheath surrounds the outside of the hair follicle and contains progenitor cells that maintain and regenerate the dermal papilla, a key component for hair growth. This has been recognized for decades as a key component of the hair growth cycle, though not fully understood. As individual hairs proceed through the life cycle, the dermal papilla cells signal to the stem cells at the root of the hair to begin producing a new hair shaft, while also arresting growth of the existing hair. When hair stops growing and moves into its destructive phase in the absence of new growth stimulation, hair loss and baldness results.

Hairs are continually shed and renewed during the full hair growth cycle. Hair grows from the follicle, underneath the skin, with off-shooting blood vessels which nourish hair shafts. Between starting to grow and falling out years later, each hair

HAIR CONTINUED ON PAGE 9

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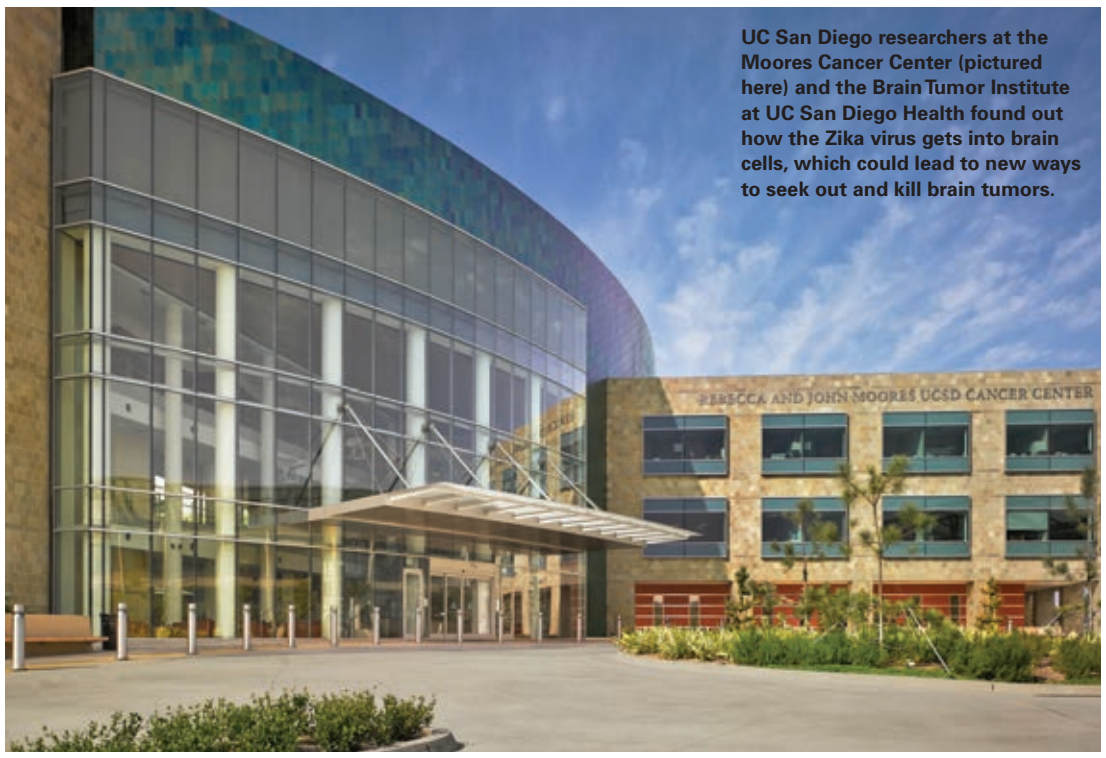
MAKING GOLD OUT OF LEAD

UC San Diego team's Zika virus discovery could lead to a new way to target brain cancer cells

BY KELSEY KAUSTINEN



UC San Diego researchers at the Moores Cancer Center (pictured here) and the Brain Tumor Institute at UC San Diego Health found out how the Zika virus gets into brain cells, which could lead to new ways to seek out and kill brain tumors.

CREDIT: UNIVERSITY OF CALIFORNIA, SAN DIEGO

SAN DIEGO—It's hard to believe anything good could come from a virus, unless you count sick days as a bonus. But deeper investigation into the nature of the Zika virus may very well have offered up a boon, thanks to work by two teams from the University of California, San Diego (UC San Diego) School of Medicine. The teams were studying the Zika virus in hopes of discovering a way of preventing microcephaly, stunted neonatal brain development caused by infection by the Zika virus. The researchers were optimistic that by determining how the pathogen gets into brain cells, they could block that avenue of access.

Their work led them to αvβ5 integrin, the molecule responsible for Zika virus' ability to entering brain stem cells. While this obviously offers a new way to protect people from Zika infection, it could also offer an unexpected secondary bonus in the form of a new method for targeting brain cancer stem cells. The teams published their work in a pair of papers, one in *Cell Press* and the other in *Cell Stem Cell*.

Integrins are molecules found on the surface of cells that play a role in cell adherence and communication. In the *Cell Press* paper, titled "Integrin αvβ5 Internalizes Zika Virus during Neural Stem Cells Infection and Provides a Promising Target for Antiviral Therapy," the authors note that "Integrins, a family of 24 heterodimers consisting of α and β subunits, are transmembrane adhesion receptors that are key components of cell signaling mechanisms involved in cancer progression and metastasis (Hynes, 2002). Specific ligands bind and cluster integrins to regulate vehicle trafficking and transduce both outside-in and inside-out signaling events (Hynes, 2002). In one of the outside-in signaling mechanisms of integrins, focal adhesion kinase (FAK) is phosphorylated and activated to recruit additional kinases and induce complex signaling cascade to regulate cell survival, proliferation, and migration (Mitra and Schlaepfer, 2006). Therefore, FAK inhibitors have been developed to control migration, invasion, and metastasis of various tumors."

Dr. Tariq Rana, professor and chief of the Division of Genetics in the Department of Pediatrics at UC San Diego School of Medicine and Moores Cancer Center, led one of the teams, who used CRISPR to delete every gene in a 3D culture of *in-vitro* human glioblastoma stem cells. They labeled the Zika virus with green fluorescent protein to make its movements more visible, then exposed each variation of the cancer cells to the virus to determine which proteins' presence was necessary for Zika to invade cells. All told, 92 human brain cancer stem cell genes were identified as necessary for Zika virus to infect and replicate in the cells, but of those, the gene that encodes the αvβ5 integrin was identified as a key culprit.

"Integrins are well known as molecules that many different viruses use as doorknobs to gain entry into human cells," Rana explained in a press release. "I was expecting to find Zika using multiple integrins, or other cell surface molecules also used by other viruses. But instead we found Zika uses αvβ5, which is unique. When we further examined αvβ5 expression in brain, it made perfect sense because αvβ5 is the only integrin member enriched in neural stem cells, which Zika preferentially infects. Therefore, we believe that αvβ5 is the key contributor to Zika's ability to infect brain cells."

The second team, led by Dr. Jeremy Rich, professor in the Department of Medicine at UC San Diego School of Medicine and director of neuro-oncology and of the Brain Tumor Institute at UC San Diego Health, took a different approach. Since integrins also serve as cellular entry points for viruses such as adenovirus, foot-and-mouth disease virus and rotavirus, they systematically inhibited each integrin with a different antibody.

What they found was that blocking αvβ5 "almost completely blocked the ability of the virus to infect brain cancer stem cells and normal brain stem cells," according to Rich. Next, they inhibited αvβ5 in a glioblastoma mouse model with either an antibody or by deactivating the gene that encodes the integrin; both approaches effectively blocked Zika infection and extended the mice's lifespans. In addition, blocking the integrin in glioblastoma tumor samples removed from human patients during surgery also blocked the infection. To further test ways of blocking αvβ5, they infected mice with Zika virus and then treated them daily with either cilengitide or SB273005, experimental cancer drugs that inhibit αvβ5. When they examined the mice six days after infection, the treated mice had half as much virus in their brains as the mock-treated mice.

To confirm these results, Rana's team is working a mouse model that is genetically designed to lack αvβ5 in the brain.

"The neat thing is that these findings not only help advance the Zika virus research field, but also opens the possibility that we could similarly block the entry of multiple viruses that use other integrins with antibodies or small-molecule inhibitors," Rana remarked.

Rich's study also provided answers for why Zika virus prefers glioblastoma stem cells over healthy brain cells. Glioblastoma stem cells produce both of the subunits that comprise αvβ5: αv (which is associated with stem cells) and β5 (which is associated with cancer cells). As well as being key to Zika virus infection, αvβ5 is also pivotal to glioblastoma stem cell survival.

Moving forward, Rich's team is working with other groups on targeted drug studies to identify drugs that can block Zika virus, in addition to exploring how genetically modifying Zika virus could allow it to more effectively target brain cancer cells without damaging healthy cells.

"While we would likely need to modify the normal Zika virus to make it safer to treat brain tumors, we may also be able to take advantage of the mechanisms the virus uses to destroy cells to improve the way we treat glioblastoma," he said. "We should pay attention to viruses. They have evolved over many years to be very good at targeting and entering specific cells in the body." ■

EDITCONNECT: E01222004

LODO

CONTINUED FROM PAGE 6

metagenomics-based small-molecule discovery platform to discover novel anti-infective agents for two global partners while building an internal pipeline of oncology drug candidates. The company expects to establish more partnerships and expand its own programs in other therapeutic areas.

According to Pfost, who was previously general partner at venture capital firm Advent Life Sciences and acting CEO of MicroBiome Therapeutics, "Pharmaceuticals derived from nature have been among the richest sources of important drugs, but productivity declined as the limitations and costs of conventional technology restricted researchers to a small pool of candidates. Lodo's platform is a game-changer. It uniquely integrates advanced technologies including NGS and AI/ML to leapfrog those limitations, providing us a historic opportunity to reinvent environmentally-sourced drug discovery."

He added, "We are the only company that can broadly access microbial DNA encoding such highly diverse collections of drug-like molecules, and we can also analyze, prioritize and enrich these molecules *in silico*, with orders of magnitude improvements in efficiency and speed. Our scientists combine deep knowledge of molecular and biological targets with computer-aided structure activity relationship data to bridge from the DNA to assessments of the encoded molecule's ability to bind to its target. This represents a quantum leap in capability compared to the laborious and costly laboratory methods required for conventional natural-product drug research. I welcome the opportunity to work with our exceptional team, top-tier partners and investors to further advance our platform and address major unmet medical needs."

Dr. Sean Brody of Rockefeller University, a pioneer in direct molecular research and a co-founder of Lodo Therapeutics, said, "More than half of all small molecule drugs for cancer, infections and type 2 diabetes today are derived from natural products, representing significant promise of this approach for patients. Our genome-based, culture-independent approach exploits the power of microbial evolution to identify therapeutically valuable natural products. With the support of Accelerator, we can tap this rich, natural source of small-molecule diversity to develop new therapies for emerging bacteria and drug resistant bacteria, critical needs in today's global healthcare environment."

In 2018, Lodo Therapeutics formed a strategic drug discovery collaboration with Genentech, a member of the Roche Group. Under the terms of the agreement, Genentech is using Lodo Therapeutics' proprietary genome mining and biosynthetic cluster assembly platform to identify novel molecules with therapeutic potential against multiple disease-related targets of interest to Genentech. Lodo, which has already received an upfront payment, is also eligible to receive research, development and commercialization milestone payments up to $969 million, based on achievement of certain predetermined milestones. In addition, Lodo stands to receive tiered royalties on sales of certain products resulting from the collaboration. ■

EDITCONNECT: E022004

PULMONARY

CONTINUED FROM PAGE 6

associated with disease and Acceleron's deep expertise in TGF-beta superfamily signaling in an effort to generate potentially disease-modifying therapeutics," Habib Dable, CEO of Acceleron Pharma, stated in a press release. "With this agreement, along with the advancement of the Acceleron-discovered assets sotatercept—in Phase 2 trials in pulmonary arterial hypertension—and ACE-1334, we underscore our growing commitment to the development of novel therapies for patients with pulmonary diseases of high unmet medical need."

Per the terms of the agreement, Acceleron gains access to Fulcrum's proprietary product engine and target identification platform to identify small molecules that control the expression of target genes implicated in pathways associated with a pulmonary disease of interest. In return, Acceleron will make a one-time, upfront payment of $10 million to Fulcrum, as well as reimbursement for relevant R&D costs. Fulcrum also stands to receive research, development and commercialization milestone payments of up to $295 million for the first product commercialized and up to a maximum of $143.5 million in additional milestone payments for any subsequent products. In addition, Fulcrum is also eligible for tiered royalty payments in the mid-single-digit to low double-digit range on net sales.

The two companies will work together to identify therapeutic targets and small-molecule drug candidates, and Acceleron will assume responsibility for all development and commercialization activities for therapeutics identified under this agreement.

"We are very pleased to partner with Acceleron on this important research initiative," remarked Dr. Robert J. Gould, CEO of Fulcrum Therapeutics. "This collaboration builds on and extends the proven potential of our platform to identify therapies that can address the root cause of diseases, including our progress with losmapimod, currently in a Phase 2 clinical trial for FSHD and extensive preclinical and early-stage research targeting other genetically defined diseases. This new opportunity to screen and identify pulmonary disease-specific therapies is another reflection of the broad potential applications of the Fulcrum platform in gene modulation."

Bryan Stuart, chief operating officer of Fulcrum, tells *DDNews* that this is the first time Fulcrum and Acceleron have worked together, and that their business relationship sprang up from a shared interest in a different rare disease.

"Our focus is around gene regulation in genetically defined rare diseases, and our lead program is for FSHD—facioscapulohumeral dystrophy, which is a very progressive and debilitating form of muscular dystrophy," says Stuart. "Through our product engine and our approach, we identified what is now our lead candidate and in Phase 2 trials for FSHD, and Acceleron previously had a program in FSHD. Through that mutual interest, we got to know Acceleron, and their understanding of our approach led to their interest in working with us on a different disease."

"As Fulcrum looks as different diseases and therapeutic areas, we plan to both develop and commercialize therapies ourselves, and at the same time, there are also other diseases where we feel it's more appropriate to work with a partner who would commercialize."

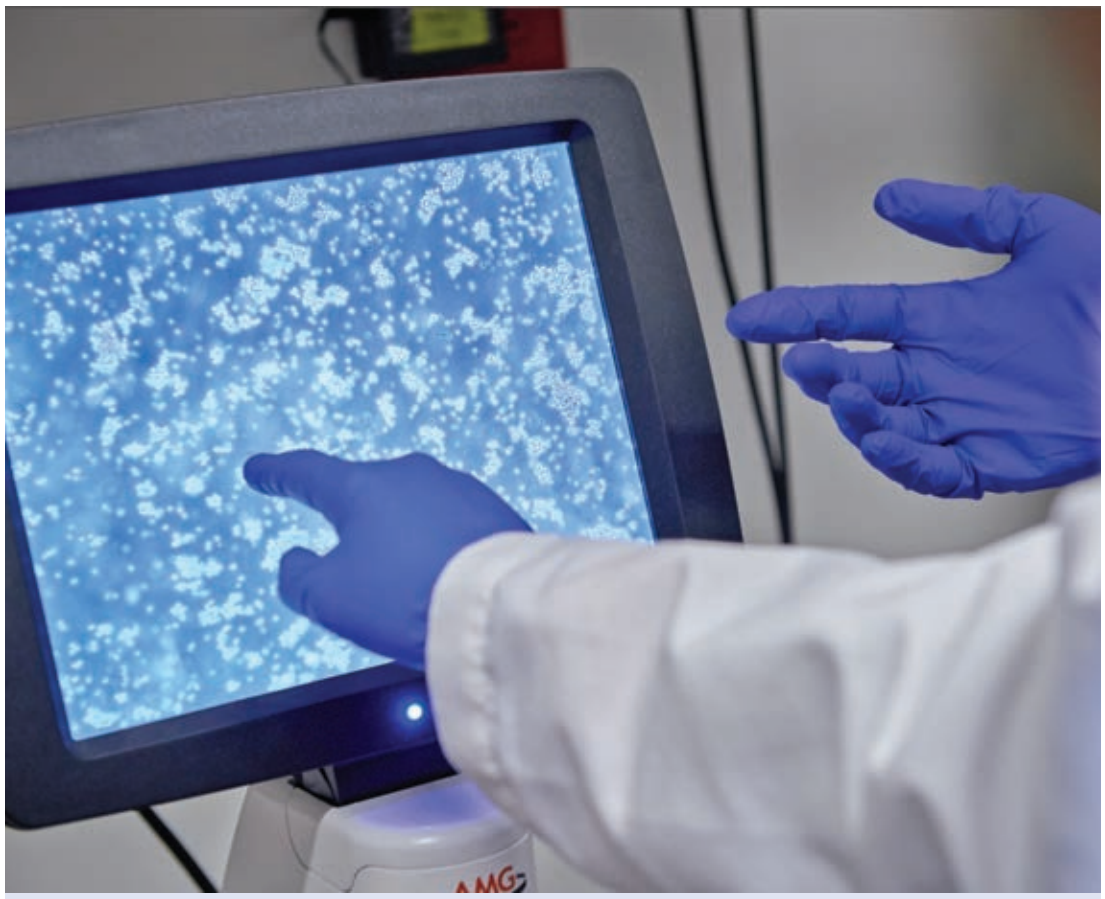
Bryan Stuart, chief operating officer of Fulcrum Therapeutics

Fulcrum's proprietary product engine identifies drug targets that can modulate gene expression in order to treat rare diseases by directly targeting the source of gene mis-expression. The company's approach combines disease modeling, scalable cell biology with custom robotics, characterization in patient-derived models and profiling of therapeutic candidates against a variety of patient-derived tissue-relevant cells.

On its end, Acceleron is advancing two pipeline candidates in pulmonary areas at present. Sotatercept is in two Phase 2 trials—the PULSAR trial and the SPECTRA exploratory trial—in pulmonary arterial hypertension, and ACE-1334 is in Phase 1 development in an undisclosed pulmonary disease.

"As Fulcrum looks at different diseases and therapeutic areas, we plan to both develop and commercialize therapies ourselves, and at the same time, there are also other diseases where we feel it's more appropriate to work with a partner who would commercialize. So we want to be very mindful of which areas we plan on building up a development and commercial presence. While we haven't disclosed the disease per se, we believe this is significant disease where we feel that with Acceleron's expertise, in terms of development in this space, this has the potential to address a meaningful unmet need in the market," Stuart concludes. ■

EDITCONNECT: E022005



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Researchers at Mount Sinai have identified a specific mechanism within the hair growth cycle that results in hair loss, leading to hope that this mechanism can be pharmacologically to slow or prevent hair loss.

HAIR

CONTINUED FROM PAGE 6

passes through four stages: anagen (growing phase), which lasts two to seven years and determines length of hair; catagen (destructive phase), a transitional phase when follicle shrinks and detaches from the dermal papilla; telogen (resting phase), which lasts +/- three months while old hairs rest and new hairs are starting to grow; and exogen (new hair phase), a constantly cycling phase when old hairs are shed while new hair continues to grow. Every hair can be at a different stage of the growth cycle at any given time.

The average life span of growing follicles in humans varies depending on hair type, and can be five to seven years for scalp hairs.

The hair cycle is a complex biological process that depends on intricate regulation of stem cell rest and activation, as well as progenitor proliferation, cell-fate choices, differentiation and cell death. Each human follicle is a regenerative adult tissue that follows this cycle, and the total amount of hairs remains constant so long as they don't get lost or communications in the cycle break down, leading to baldness.

"The hair-growth cycle is asynchronous," explains Dr. Michael Rendl, the associate director of the Black Family Stem Cell Institute at the Icahn School of Medicine at Mount Sinai. "We don't know what kicks in the destructive phase, or what underlying 'clock' is at work."

"Our major discovery is a previously unknown smooth muscle that surrounds hair follicles and is called dermal sheath. Its contraction is important for moving the instructive niche, *i.e.* dermal papilla cells, to the stem cells for growth of a new hair in the cycle. This type of muscle cannot be controlled voluntarily, similar to the ones in blood vessels, but we can control it by drugs that can block contraction. We are excited about the possibility to develop methods for blocking sheath contraction, stopping follicle regression and preventing the loss of the existing hair before a new hair can grow. Our studies continue to make this possible in the future," he adds.

According to Rendl, researchers will need to conduct many more studies exploring their ability to safely block the contraction of the dermal sheath to answer some resulting questions. Would halting this process result in the evergreen presence of an old hair, thus eliminating the need for haircuts? How would a hair shaft hold up under such longevity? Would old and stagnant hair be preferable to baldness? Considering the stigma associated with hair loss for both men and women, many people will be watching the future of this research with great interest. ■

"Our major discovery is a previously unknown smooth muscle that surrounds hair follicles and is called dermal sheath ...This type of muscle cannot be controlled voluntarily ...We are excited about the possibility to develop methods for blocking sheath contraction, stopping follicle regression and preventing the loss of the existing hair before a new hair can grow," says Dr. Michael Rendl, the associate director of the Black Family Stem Cell Institute.

EDITCONNECT: E022006

Editor's Focus: Breaking down the outbreak

BY JEFFREY BOULEY

Jeffrey Bouley, *DDNews* Chief Editor

SO, YOU MIGHT HAVE HEARD of this little thing called the Wuhan coronavirus—I know it isn't being covered much in the news, but it's possible you might have heard something about it. Maybe just a little. Or more likely a ton. And possibly much of it misinformation and panicky hype.

In all seriousness, this isn't a story that's flying under the radar; instead, it's crashing right into us at high velocity. My 14-year-old daughter asked me very recently, "Am I going to die from the coronavirus?" and rarely have I ever been so glad to be a longtime career healthcare-medical-pharma journalist as I put some of the media and internet hyperbole into perspective for her. Certainly perspective is needed for some people, given that apparently there is a contingent of folks out there who think the virus is spread via the Corona brand of beer.

I'm not saying this is an infectious outbreak that should be taken lightly. Quite the opposite—I appreciate a vigorous response to public health risks. It's just that so far, influenza (the flu also being a coronavirus, by the way) remains the bigger health risk.

Still, there are concerns. This particular coronavirus—technically known as 2019-nCoV right now, and also known as the Wuhan coronavirus because of the Chinese city in which it originated in December—should be taken seriously. The number of confirmed cases in China and 23 other countries has risen to at least 14,380, according to data from the World Health Organization, surpassing the number in the 2002-2003 outbreak of severe acute respiratory syndrome (SARS). But let's remember that we survived SARS, which so far seems to lead to a higher percentage of deaths than the Wuhan virus. Also, as of Feb. 1, Chinese officials had reported 304 deaths from the Wuhan virus, compared to thousands already from the more common flu in the United States alone since influenza season started.

But while perspective is good, wariness doesn't hurt either, and this is shaping up to be a pandemic. Everyone should be doing what they can, from people doing their best not to spread infections by washing their hands and covering up when they cough or sneeze, all the way to life-sciences folks rushing to create vaccines and diagnostics.

"I'm not saying this is an infectious outbreak that should be taken lightly. Quite the opposite—I appreciate a vigorous response to public health risks. It's just that so far, influenza (the flu also being a coronavirus, by the way) remains the bigger health risk … Still, there are concerns."

And in that vein, we have a commentary on the next page talking about what's being done and lessons that can be learned for the drug discovery world (and other life-sciences professionals) from this virus, and we have devoted the entire "Late-breaking News" section on page 38 to recent news related to the Wuhan coronavirus and pertinent to you, our readers.

Stay safe and healthy out there. ■

EVERYTHING IS TOO EXPENSIVE: PART 2

BY PETER T. KISSINGER

PHARMA WAS OFFENDED by my December column and they boosted prices as a 2020 New Year's resolution. It is difficult to precisely know what they did because the public can't yet see how such announcements percolate through to patients. Will the new cash support innovative R&D, cover manufacturing cost increases, support advertising, improve the dividend, or be the means to announce deeper discounts or rebates to selected channels? That will vary company to company and drug to drug. Average price increases have no meaning for patients. Impeach averages for their tyranny.

Peter T. Kissinger, Purdue University

Pricing is a variable. We in business want to maximize the sales from top payers while making incremental profit at the low end. That's fair. Wine is a popular drug with pricing that varies with where you buy it and when. Airlines and hotels do the same—optimize the mix, fill capacity. Volume matters, and some states are exploring their own negotiations with manufacturers. In the generics area one can imagine several companies competing for supply contracts for different medications, with one of them winning and others losing. That's OK. With proprietary drugs, it's tougher, but we should do a better job of thinking about comparative advantage relative to price. Given that results for many clinical trials are never published, how can we fairly evaluate safety and efficacy?

A presidential candidate promises to lower drug prices on the first day in office. Others now suggest the FDA is less rigorous with approvals than before. There is such a thing as being between a rock and a hard place, a "mission impossible" assignment. (Perhaps Tom Cruise is available.) The market sets prices. Too high and sales head to zero; too low and we can't cover production costs and shortages result.

In response to the December column, several astute readers noted that I'd failed to mention that pharma is "raking in billions in profit" from research sponsored by the government, for example, at universities. Whoa! That's wildly out of context. Academic research is high-risk stuff for the most part, and employees of biopharma are paying for it like the rest of us. It is done principally to educate students who start as amateurs in the lab and emerge as professionals. The chance of an outcome quickly translatable to patients is extremely low. The basic biology of disease is unraveled when we are lucky and is then shared globally for all who can use it.

We can't discover more than a "potential drug" or "potential drug target." It will not *be* a drug until the FDA says so, often 10 to 20 years later. These days, the next step is often to put the academic therapeutic concept into a startup or small biopharma with no sales at all. They will operate at a total loss on the project for a very long time. Most of these firms will also fail. Some will progress a bit and entice established pharma to fund the work further (typically for an early clinical phase), pursue a license agreement, or buy the company outright. There is no formula, no process that works consistently. Those who think that academics develop new drugs are reading too many university press releases.

A very nice read on a translational project that brought together academics, other nonprofits, government agencies and pharmaceutical companies was published online in *STAT* on Jan. 7, titled "Against all odds: The inside story of how scientists across three continents produced an Ebola vaccine" by Helen Branswell. Twists, turns and never-give-up stubbornness over decades is not atypical. That's what it often takes. Merck jumped in because they could and saw the need to serve. Public-private partnerships are becoming more common, especially with respect to orphan diseases and those most prevalent in developing economies. Resilience in the face of the negative cash flow from R&D is stressful. Today a lot of the discovery risk is outsourced, and the validation of safety and efficacy is as well. We need the BIG(!) pharma infrastructure to manage the many of hundreds of millions required. Academics can only take tiny risks, reload and repeat. They don't lose a thing, not even a dissertation chapter. All research projects provide a result, rarely a therapy.

Another reaction to the December column related to healthcare being a right. I disagree. It is certainly desirable, but health is also a responsibility and a matter of luck. Your luck is improved when you consider "better living through less chemistry and more exercise" (paraphrasing an old DuPont tagline). Also consider the dogma that some 50 percent of prescriptions are never filled. Those that are filled are too often picked up by patients who are then not adherent to their doctor's recommendations. Docs used to give "orders." Today they are our paid consultants. To intelligently accept our consultant's wisdom, we need to read product inserts and study the

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COMMENTARY: Learning from the Wuhan coronavirus

Collaboration leads the way to better understanding of pathogen

DR. BARRY BUNIN OF COLLABORATIVE DRUG DISCOVERY INC.

AS NEWS ABOUT THE WUHAN CORONAVIRUS (2019-nCoV) dominates the headlines, it is easy to get emotional and react to every latest development. However, we believe it is helpful to examine the facts and take a holistic view on this outbreak.

2019-nCoV is a coronavirus, the family of viruses traditionally associated with the common mild cold. It is genetically most related to, yet distinct from, the severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) coronaviruses.

Researchers are evaluating countermeasures for 2019-nCoV using SARS-CoV and MERS-CoV as prototypes. For example, platform diagnostics are being rapidly adapted to include 2019-nCoV, allowing early recognition and isolation of cases. Broad-spectrum antivirals such as remdesivir, an RNA polymerase inhibitor, as well as lopinavir/ritonavir and interferon beta have shown promise against MERS-CoV in animal models and are being assessed versus 2019-nCoV. Vaccines, with nucleic acid vaccine platform approaches used for SARS-CoV or MERS-CoV, are being pursued at the National Institute of Allergy and Infectious Diseases Vaccine Research Center.

Coronavirus vaccine development

Vaccine (and antibody) development makes sense, given the potentially faster timeline than *de-novo* small-molecule drug discovery, although other antivirals have been used in SARS and MERS. The *Wall Street Journal* reported several drugmakers are racing to develop vaccines that could protect against the new respiratory virus originating in China. Moderna Inc., Inovio Pharmaceuticals Inc. and Novavax Inc. all plan to develop vaccines against the newly identified viral strain. Researchers at the University of Queensland in Australia are also trying to develop a vaccine against the strain.

More recently, FierceBiotech reported that both JNJ and Gilead have jumped into the accelerated coronavirus vaccine race.

"One of the unique ways we can combat epidemics, not available to previous generations, is to leverage the free, global, instantaneous access to everyone across our species via the internet. We have only scratched the surface of the full potential of this mechanism for both response and research."

Lessons for drug discovery collaboration?

As shared in a timely NIH *JAMA* Viewpoint from Drs. Catharine I. Paules, Hilary D. Marston, and Anthony S. Fauci, we know 2019-nCoV is similar to MERS and SARS thanks to rapid data sharing and international collaboration: "While MERS has not caused the international panic seen with SARS, the emergence of this second, highly pathogenic zoonotic HCoV illustrates the threat posed by this viral family. In 2017, the WHO placed SARS-CoV and MERS-CoV on its Priority Pathogen list, hoping to galvanize research and the development of countermeasures against CoVs. The action of the WHO proved prescient. On December 31, 2019, Chinese authorities reported a cluster of pneumonia cases in Wuhan, China, most of which included patients who reported exposure to a large seafood market selling many species of live animals. Emergence of another pathogenic zoonotic HCoV was suspected, and by January 10, 2020, researchers from the Shanghai Public Health Clinical Center & School of Public Health and their collaborators released a full genomic sequence of 2019-nCoV to public databases, exemplifying prompt data sharing in outbreak response."

Publishers like the *British Medical Journal* (and, in a moment of solidarity, other publishers like Wiley and Elsevier) are providing information on the coronavirus freely on the internet to spur short-term global response efforts and support long-term research, in contrast to their usual paid-content business models. The British Medical Journal has also made information freely available on MERS and SARS.

One of the unique ways we can combat epidemics, not available to previous generations, is to leverage the free, global, instantaneous access to everyone across our species via the internet. We have only scratched the surface of the full potential of this mechanism for both response and research.

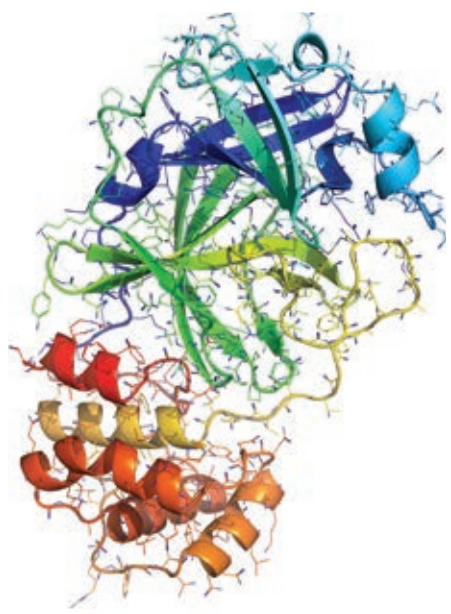
Collaboration can range from two scientists sharing data privately to publicly shared data with the international scientific community. Quantity has a quality all its own. In the case of an outbreak, publicly shared information allows the conversation to co-evolve with many brains (and technologies) rapidly in parallel—when additional data, analyses and insights are also shared in a timely manner.

When a timely response is needed, collaboratively sharing data allows the rate of learning to accelerate.

Within the commercial drug discovery arena, there are two counterbalances to immediate sharing. First, the data from diverse drug discovery assays are heterogeneous, complex and may require metadata from procedures to understand. Second, the data sharing, due to this heterogeneity requires sophisticated tools (*i.e.* sharing structure activity relationships from a series of primary and secondary high-throughput screens run on hundreds of thousands of compounds, at nine concentrations, in triplicate is not as trivial as, say, sharing a like on Facebook). Nonetheless, collaboration may be the key to quantum leaps in efficiency in drug discovery.

Open data (and idea) sharing is the purpose of the scientific literature. Scientific literature became a more global phenomena with the advent of the printing press.

We take the internet for granted today. However, the ability to instantaneously share information around the world is arguably the most fundamental paradigm shift for our species. We are no longer ants, but an ant colony. We can learn from the art of emergent, collective intelligence. Our memes traveling at the speed of the www to coordinate our collective thinking is our competitive advantage vs. the ancient relentless mechanisms of mutation, selection and horizontal gene transfer. The ace in our pocket is the ability to collectively learn and instantaneously share



Phyre2 model ribbon diagram rendering of the 2019-nCoV coronavirus (the Wuhan coronavirus) protease as target for antiviral drugs. (Rendering by 分液漏斗 and used under the Creative Commons Attribution-Share Alike 4.0 International license.)

collective learnings. Prokaryotes have a fixed velocity of learning and information transfer (different in every case, but metaphorically speaking in general). Humans combining our intelligence with the Internet have the potential for uncapped, accelerated learning.

The next level of accelerated learning is integrating computers and algorithms together, via web-based platforms. Not only our own CDD Vault, which balances protecting intellectual property through secure data sharing while promoting maximum collaboration, but all the connecting web-based scientific data sharing platforms (with the majority sponsored by our publicly funded, government coordinated efforts such as PubMed, GenBank, ChEMBL, KEGG and PubChem, to mention just a handful of many impactful, web-based scientific data-sharing platforms). And there are highly impactful, community based efforts such as, well, Wikipedia (and its equally important cousin, DBpedia). We can and will collaborate better over time.

There is a need for accelerated data sharing and discovery for a number of viral diseases, including 2019-nCoV.

It is worth mentioning the rapid development of 2019-nCoV diagnostic kits, a number of which are already now available.

As with the response to the last Ebola epidemic and after this 2019-nCoV epidemic, we will need to consider general solutions to surveillance and response. The only thing we know for sure is that next time will be slightly different. In response, our tactics and tools can get better with each new epidemic via greater, web-coordinated collaboration.

In the near future, it is not difficult to imagine a time when emerging data and protocols are represented in FAIR (findable, accessible, interoperable, reusable) standardized formats for parallel computer analyses. Bioportal already has standardized, precisely defined terms for the new coronavirus. Future generations will be able to collaborate better, faster, longer term and smarter. We're all in this together. ■

Adapted from "Coronavirus (2019-nCoV): The Facts" article at the Collaborative Drug Discovery Inc. website (www.collaborativedrug.com). You can link to the full article at www.collaborativedrug.com/coronavirus-2019-ncov-facts

EXPENSIVE

CONTINUED FROM PAGE 10

results of clinical trials, at least for the most critical diseases. Most in our community suggest that only we, not the patients, can appreciate what's going on. That's arrogant and unfair. We should no longer expect to thrive on a mix of hype and obscurity. Boeing again comes to mind. Cutting corners and keeping secrets needs to go away.

The meaning of "ethical pharmaceutical company" may need to be updated. There is a lot of stress in the system. We now know more. The patients should know more too and adjust their expectations. Medicine is a team sport, dramatically different from before Y2K and with very little in common from the 1950s and 60s. The decade now ended was enormously productive in delivering results for patients. We'll do even better in this one. Please remember that there are no drugs that are "safe and effective" in every patient or in *any* patient at *any* dose. ■

Peter T. Kissinger (who can be reached at kissinger@ddn-news.com) is a professor emeritus at Purdue University, founder of BASi, chairman of Phlebotics and director of both Prosolia and Tymora.

To read the first "Everything is too expensive" column from the December 2019 issue, go to http://ddn-news.com/index.php?newsarticle=13833

RESEARCH & DEVELOPMENT

BRIEFS

Targeting retinal vascular disease

CAMBRIDGE, U.K.—Biotechnology company Exonate shared news last month of a strategic collaboration agreement with Janssen Pharmaceuticals Inc., one of the Janssen Pharmaceutical Companies of Johnson & Johnson, to develop an eye drop treatment for retinal vascular diseases such as wet age-related macular degeneration and diabetic macular edema using mRNA-targeted therapies. Exonate's pipeline includes small molecules that inhibit the production of pro-angiogenic vascular endothelial growth factor (VEGF) via selective inhibition of serine/threonine-protein kinase-mediated VEGF splicing.

Dr. Catherine Beech, CEO of Exonate, said: "I am absolutely delighted to enter this strategic collaboration with Janssen; we are looking forward to successfully developing a novel treatment for retinal neovascular diseases."

BioMed X, Boehringer Ingelheim join forces

HEIDELBERG, Germany—BioMed X and Boehringer Ingelheim have kicked off a new joint research group at the BioMed X Innovation Center in Heidelberg that will investigate myelination deficits in the adolescent brain and their connection to the development of schizophrenia. As the human body matures, the brain is reorganized in a variety of ways, including cortical myelination, dendritic arborization, synaptic pruning and circuit plasticity. Evidence has shown that genetic, epigenetic and environmental factors can adversely affect this process and increase risk for schizophrenia. This new effort will look specifically into myelination deficits, developing *in-vitro* and *in-vivo* platforms to assess oligodendrocyte development and myelination, with a goal of identifying novel neuronal and oligodendrocytic factors that impact myelination as possible targets for preventing the development of schizophrenia.

IN THIS SECTION

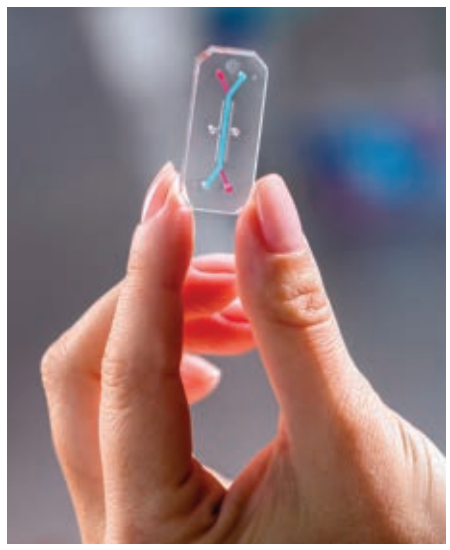
'A leading-edge preclinical testing method'

Intestine-on-a-Chip promises better personalized medicine

BY KRISTEN SMITH

BOSTON—Emulate Inc. has expanded its Organs-on-Chip library to include an initially successful Duodenum Intestine-Chip, which appears to recreate true-to-life functions of the small intestine and colon. The chip is created using endoscopic biopsies of healthy adult human donors coupled with primary human intestinal microvascular endothelial cells derived from human small intestine. When populated with organoids, these chips appear to outperform organoids alone as a mechanism to predict human response to various drugs.

As with each of Emulate's Organ-Chips—for organs including the lung, liver, brain or kidney—the Intestine-Chip is lined with tens of thousands of living human cells and tissue, and then integrated within the instrumentation of their Human Emulation System to recreate the true-to-life physiology that cells experience within the human body. While Emulate's chip design is universal, the cells within each Organ-Chip and the tuning of the surrounding instrumentation are customized to reflect the distinct biology of each human organ, allowing a more reliable platform through which to study disease and pharmacological interventions.



CREDIT: EMULATE INC.

While Emulate's chip design is universal, the cells within each Organ-Chip and the tuning of the surrounding instrumentation are customized to reflect the distinct biology of each human organ, reportedly allowing a more reliable platform through which to study disease and pharmacological interventions.

In a study conducted in partnership with Johns Hopkins School of Medicine and published in the journal *eLife*, researchers found two essential elements of the Intestine-Chip's functionality. First, the Intestine-Chip produced a nearly identical genetic signature at the transcriptomic level compared to human intestine duodenum tissue, showing its ability to emulate the human intestine tissue for highly predictive drug assessment. Second, it showed that the biology of important drug transporters and drug metabolizing enzymes of the intestine remained intact in the Intestine-Chip, which opens up new testing capabilities beyond current animal testing because of the unique human species-specific nature of these drug transporters and enzymes.

CHIP CONTINUED ON PAGE 13

Ras, Raf and recall

Scripps Research team uncovers the genes that play a role in cementing experiences as long-term memories

BY KELSEY KAUSTINEN

JUPITER, Fla.—It's well known that short- and long-term memories are stored in certain parts of the brain, but the fact that specific genes play a role in long-term memory, not just specific lobes, is likely news to many. Prof. Ronald Davis of Scripps Research, Florida, and his lab detailed in a recent publication how Ras and Raf both play a role in the process of memories transitioning from short-term to long-term storage in the brain. Their work was published in the *Proceedings of the National Academy of Sciences* (*PNAS*) in a paper titled "Ras acts as a molecular switch between two forms of consolidated memory in *Drosophila*."

The research focused on a type of memory known as

SCRIPPS CONTINUED ON PAGE 14

CREDIT: SCRIPPS RESEARCH

Prof. Ronald Davis of Scripps Research, Florida, and his lab detailed in a recent publication how Ras and Raf both play a role in the process of memories transitioning from short-term to long-term storage in the brain.

CREDIT: UNIVERSITY OF PENNSYLVANIA

The University of Pennsylvania (pictured here) has partnered with Eagle Pharmaceuticals to explore the development of Ryanodex (dantrolene sodium) for the potential treatment of people living with Alzheimer's disease.

New uses for Ryanodex

Eagle and UPenn explore drug's potential to treat Alzheimer's

BY JENNIFER CLIFFORD

WOODCLIFF LAKE, N.J.—Last month, Eagle Pharmaceuticals announced a new exclusive worldwide license agreement with the University of Pennsylvania under which they will explore the development of Ryanodex (dantrolene sodium) for the potential treatment of people living with Alzheimer's disease. This agreement includes terms for funding additional research and provisions regarding commercialization of products developed under the license.

"Our collaboration with University of Pennsylvania builds on Eagle's strategy to develop and commercialize therapies for

EAGLE CONTINUED ON PAGE 15

CHIP

CONTINUED FROM PAGE 12

Together, these findings show that the Intestine-Chip offers a technology for more human-relevant and robust system to better predict pharmacokinetics and drug-drug interaction.

"One of the most compelling findings from this published research is the demonstration that intestinal organoids function extremely well in the Intestine-Chip," according to Geraldine A. Hamilton, president and chief scientific officer of Emulate. "Emulate's Intestine-Chip recreates the biology of the human intestine by taking advantage of intestinal organoids, which are generated from biopsies and contain multiple cell types, immune cells, microbiota and intricate tissue structures. The Intestine-Chip provides the microenvironment in which these organoids maintain their 3D structure and immune cell function. We see the value of using our Intestine-Chip product with organoids as a leading-edge preclinical testing method."

Efforts to imitate the intestinal biome for research purposes are not new. A variety of approaches have yielded useful models, but none of them have successfully accounted for the vast differentials in the dynamic and complex intestinal microenvironment. Emulate's Duodenum Intestine-Chip, currently under development with a rollout planned this year, is demonstrating a robust ability to accurately recreate human intestine tissues for highly predictive and human-relevant preclinical drug assessment.

"Using our Intestine-Chip, we are able to accurately recreate key functions of the human duodenum. These findings show a path forward to using a more human-relevant and robust system to better predict pharmacokinetics and drug-drug interaction," said Hamilton. "Today, we see the value of using our Intestine-Chip product with organoids as a leading-edge preclinical testing method. Further in the future, we envision exciting potential applications for our Intestine-Chip to utilize cells isolated from individual patients to be used for personalized medicine."

According to the *eLife* paper, the Chip appears to succeed where other models have failed in a variety of areas. Emulate successfully applied mechanical forces to recapitulate the blood flow and shear stress which improved the formation of polarized cytoarchitecture and the appearance of intestinal microvilli on the apical cell surface. The Chip also supported successful maturation of all major intestinal epithelial cell types in the physiologically relevant ratios and demonstrated low paracellular permeability.

Importantly for its use in pharmacokinetic studies, it more closely mimics *in-vivo* expression of drug uptake and efflux transporters and exhibits the correct luminal localization and functional activity observed in the human duodenal tissue. Researchers also found that the organoid-derived intestinal cells can be combined with Organs-on-Chips technology to provide a robust and human-relevant system for preclinical assessment of CYP450-mediated metabolism, activity of drug transporters, and the potential risk of drug-drug interactions.

The study authors are very hopeful about the future utility of the Duodenum Intestine-Chip in personalized medicine, as noted in the conclusion of the paper: "As [the Chip] is composed of cells isolated from individual patients, it could be personalized as needed, in order to assess interindividual differences in drug disposition and responses, study the effect of genetic polymorphisms on pharmacokinetics and pharmacodynamics, as well as decoupling the effect of various factors such as age, sex, disease state, and diet on metabolism, clearance, and bioavailability of xenobiotics. This system could also help us to better understand the basic biology of human intestinal tissue in healthy and disease states and potentially enable novel therapeutic development as we further our understanding of the mechanisms driving key disease phenotypes." ■

CREDIT: EMULATE INC.

"One of the most compelling findings from this published research is the demonstration that intestinal organoids function extremely well in the Intestine-Chip," according to Geraldine A. Hamilton, president and chief scientific officer of Emulate.

EDITCONNECT: E022008

"It is important to understand how a healthy cell develops to be able to decode what goes wrong in diseases," says Dr. Vijay Tiwari of the Wellcome-Wolfson Institute for Experimental Medicine at Queen's University Belfast. "Our study is the first of its kind to provide insight into the role physical DNA features play in proper development of specific cell-types of the body and how their malfunctions may underlie diseases."

CRACKING THE CODE OF GENE REGULATION

Queens University Belfast looks into how regulators are chosen from DNA and what that means for disease risk

BY JEFFREY BOULEY

BELFAST, U.K.—Within the vast genetic landscape of the human body, only certain DNA elements are chosen to regulate gene expression. Researchers at Queen's University Belfast looked into the "how and why" of this in part to better understand how this process predisposes people for certain conditions. They believe they have made a breakthrough discovery that could open the door for better and earlier diagnostics, possibly before symptoms of disease arise.

As described in the summary of the paper titled "Deciphering the Gene Regulatory Landscape Encoded in DNA Biophysical Features" and published in the interdisciplinary journal *iScience*, "Gene regulation in higher organisms involves a sophisticated interplay between genetic and epigenetic mechanisms. Despite advances, the logic in selective usage of certain genomic regions as regulatory elements remains unclear. Here we show that the inherent biophysical properties of the DNA encode epigenetic state and the underlying regulatory potential. We find that the propeller twist (ProT) level is indicative of genomic location of the regulatory elements, their strength, the affinity landscape of transcription factors, and distribution in the nuclear 3D space."

The Queens University team notes that diseases are often the result of things going wrong within a cell or set of cells within the body, and previous research has determined that many of these diseases result from mutations on a certain part of the DNA strand known as an "enhancer." In essence, the enhancers serve as a switch to be turned on in gene expression and activate the promoter region of a particular gene.

And here is where the ProT aspect comes in. ProT levels represent the angle of twisting of two neighboring DNA bases along the DNA axis, much like the propeller blades of an airplane. The Queens University researchers reportedly are the first to discover that because of high ProT levels, the surface of these enhancer sections on the DNA strands are more physically accessible and flexible than their counterparts, thus allowing easier access for DNA binding regulatory proteins. The same properties potentially make these enhancer regions more prone to be affected by mutagenic agents to harm cells and cause certain diseases, such as cancer.

"These findings answer many fundamental biological questions around the function of DNA in health and disease," said Dr. Vijay Tiwari of the Wellcome-Wolfson Institute for Experimental Medicine at Queen's University Belfast and lead author on the paper. "It is important to understand how a healthy cell develops to be able to decode what goes wrong in diseases. Our study is the first of its kind to provide insight into the role physical DNA features play in proper development of specific cell-types of the body and how their malfunctions may underlie diseases."

The researchers also discovered that as cells become abnormal, they switch to using low ProT regions as enhancer elements. These observations open novel avenues to understand the aetiology of human diseases and potentially develop an early diagnosis.

"This could mean we could look at the enhancer section of DNA in any cell of a healthy person and predict their chance of developing disease long before signs and symptoms appear," noted Tiwari. "This could result in many lives being saved, as we can use this tool to make earlier and better disease predictions, reduce disease progression and improve patient outcomes."

As noted by the authors in the paper, "Several laboratories have attempted to employ computational approaches to predict enhancers based on sequence information. Although these methods were able to predict enhancers to a certain degree, they were unable to decipher the underlying code that drives enhancer selection and strength … We discover that the ProT levels can reveal the location of enhancers, their strength, the affinity landscape of transcription factors, and distribution in the nuclear 3D space with high accuracy. Using experimental assays including single-molecule AFM imaging measurements, we show that indeed high ProT levels cause increased DNA flexibility and surface accessibility and may potentially explain their usage as regulatory elements. Furthermore, ProT levels also determine the effectivity landscape of the genome to tolerate mutations. Altogether, this work reveals the gene regulatory landscape encoded in the basic genetic sequence features and provides a significant advance in unfolding the mysteries of genetic code."

According to Queens University Belfast, the classical methods to identify enhancers have been cumbersome. But these new findings argue that identifying high ProT levels is a deterministic feature of enhancers; thus, the researchers hope this discovery will also save resources and time for scientists across the globe in identifying these gene regulatory elements critical in normal and diseased states. ■

EDITCONNECT: E01222003

SCRIPPS

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"protein-synthesis dependent long-term memory," or PSD-LTM, and used *Drosophila melanogaster* (fruit flies) for their models. Using RNA interference, the researchers lowered the expression of several genes in the brains of flies, and found that lowering the expression of the Ras gene and Raf, a downstream molecule, led to two results: intermediate-term memories were significantly enhanced while PSD long-term memories of a negative experience were eliminated entirely, according to Davis.

"Long-lasting, consolidated memories require not only positive biological processes that facilitate long-term memories (LTM) but also the suppression of inhibitory processes that prevent them," the authors explain. "The mushroom body neurons (MBn) in *Drosophila melanogaster* store protein synthesis-dependent LTM (PSD-LTM) as well as protein synthesis-independent, anesthesia-resistant memory (ARM). The formation of ARM inhibits PSD-LTM but the underlying molecular processes that mediate this interaction remain unknown."

Or, put another way, a memory can either be shuffled into intermediate storage or long-term storage, but not both.

To test the flies' memories, the researchers exposed them to certain odors in one part of a glass tube while simultaneously administering a shock to the flies' feet, thereby associating the odor with a negative experience and leading to a tendency in the flies to avoid the odor when exposed in the future. However, Dr. Nathaniel Noyes, a research associate in the Davis lab and first author of the *PNAS* paper, noted that when Ras and Raf were knocked down, the flies consistently forgot the association of the odor with the shock, regardless of how many times they'd been exposed to that series of events previously.

"Here, we demonstrate that the Ras→Raf→rho kinase (ROCK) pathway in MBn suppresses ARM consolidation, allowing the formation of PSD-LTM. Our initial results revealed that the effects of Ras on memory are due to postacquisition processes," the authors reported. "*Ras* knockdown enhanced memory expression but had no effect on acquisition. Additionally, increasing Ras activity optogenetically after, but not before, acquisition impaired memory performance. The elevated memory produced by *Ras* knockdown is a result of increased ARM. While *Ras* knockdown enhanced the consolidation of ARM, it eliminated PSD-LTM. We found that these effects are mediated by the downstream kinase Raf. Similar to *Ras*, knockdown of *Raf* enhanced ARM consolidation and impaired PSD-LTM … We conclude that MBn Ras/Raf inhibition of ROCK suppresses the consolidation of ARM, which permits the formation of PSD-LTM."

This work also identified the Ras enzyme Ras85D as a key player in the establishment of long-term memories. The team found that Ras85D is pivotal in determining whether some experiences become intermediate memories that fade or long-term PSD memories. Noyes theorized that further research will show that dopamine is also a factor in this process.

"We believe that dopamine signals to the brain that this memory is important enough to be stored long-term. We speculate that Ras and Raf receive this dopamine signal and thereby block intermediate memory and promote PSD long-term memory," he explained.

Noyes added that additional study will be required to determine exactly how closely their *Drosophila* results translate into human memory.

Davis' lab is working on a variety of other projects related to memory in *D. melanogaster* as well, among them a survey of memory suppressor genes identified through an RNAi-expression based behavioral screen, as noted on the lab's website. As "genes are generally well conserved between *Drosophila* and human," these suppressor genes could offer answers or even drug targets in humans.

The lab is also exploring memory with relation to aging. While it's well known that human memory deteriorates with age, previous research in the Davis lab revealed that in *Drosophila*, it's intermediate-term memory specifically that is compromised, "and that activating a specific neuron known as the dorsal posterior medial neuron (DMPn) reverses this impairment. This suggests an age-dependent defect in DPMn function or connectivity. In addition, protein-synthesis-dependent long-term memory is also impaired in aged flies, and this impairment might also be due to lowered function or connectivity of DPMn with mushroom body or other neurons. We are continuing our aging studies with a focus on the DPMn and how age alters its function and connectivity." ■

EDITCONNECT: E022009

B CELLS

CONTINUED FROM PAGE 1

trial sponsored by MD Anderson's Melanoma Moon Shot. The researchers also studied a group of patients with metastatic RCC being treated with neoadjuvant checkpoint blockade as part of a clinical trial led by Dr. Padmanee Sharma, a professor of genitourinary medical oncology and immunology, and Dr. Jianjun Gao, an associate professor of genitourinary medical oncology.

In each cohort, the expression of B cell-related genes was significantly higher in responders and predictive of response to checkpoint blockade. An analysis of curated melanoma samples from The Cancer Genome Atlas, in which high expression of B-cell markers was associated with significantly improved overall survival, corroborated the findings.

CREDIT: MD ANDERSON CANCER CENTER

"These results suggest there may be new ways of predicting responses to immunotherapy by including B cells as a novel biomarker," says Dr. Hussein Tawbi of the MD Anderson Cancer Center of recent oncology research results. "Perhaps most exciting is this also opens up the possibility for a therapeutic targeting of B cells in ways that could identify new avenues for treating these patients."

"There is a great need to identify biomarkers of response to therapy, and these data may allow for future studies focused on developing composite biomarkers that represent both the T- and B-cell responses," explained Sharma.

Researchers determined that B cells were localized in TLS, and the density of B cells and TLS in the tumor was higher in responders. Analysis of these infiltrating B cells showed that those in responders expressed more markers of mature and differentiated B cells, like memory B cells and plasma cells.

"Through these studies, we find that B cells are not just innocent bystanders, but are themselves contributing in a meaningful way to the antitumor immune response," pointed out first author Dr. Beth Helmink, a fellow in surgical oncology.

Wargo also collaborated on another study led by Dr. Göran Jönsson and researchers at Lund University in Sweden. That study analyzed a group of patients with metastatic melanoma, and also suggests an important role for B cells within TLS. The researchers report that the B cells may be producing tumor-specific antibodies that could be used to enhance checkpoint blockade.

According to the authors, "In this cohort of patients treated with anti-CTLA4, the TLS signature is independent of mutational load. Moreover, the TLS signature was significantly associated with overall survival in a previously published dataset of pretreatment samples from 69 patients who were undergoing anti-PD1 monotherapy or anti- CTLA4 and anti-PD1 combination therapy … we performed meta Cox regression analysis across the four cohorts treated with ICB, using multiple immune signatures: of these, our TLS signature performed best. The TLS signature was also independent of tumour mutational load in the cohort treated with anti-PD1, consistent with previous studies that have shown that immune gene signatures are not correlated with mutational load."

CREDIT: MD ANDERSON CANCER CENTER

According to researchers at The University of Texas MD Anderson Cancer Center, the likelihood of a patient responding to immune checkpoint blockade may depend on B cells in the tumor, located within specialized immune cell clusters known as tertiary lymphoid structures.

As for soft tissue sarcomas (STS), they were previously thought to be refractory to immunotherapy, but profiling of STS established five distinct classes of the disease that predict survival outcomes and responses to checkpoint blockade. Those with the best outcomes were marked by enrichment of B cells within TLS in the tumor, according to results published in January.

The study was led by Dr. Wolf Fridman and a team from Inserm, together with Dr. Hussein Tawbi, an associate professor of melanoma medical oncology at MD Anderson.

"These results suggest there may be new ways of predicting responses to immunotherapy by including B cells as a novel biomarker," noted Tawbi. "Perhaps most exciting is this also opens up the possibility for a therapeutic targeting of B cells in ways that could identify new avenues for treating these patients."

The researchers profiled expression of immune-related genes in more than 600 sarcoma samples. The resulting classifications grouped sarcomas into five classes, ranging from "immune desert" to "immune high" tumors.

"Here, we found the CD8+ T cell signature and PD1 were expressed in class D and E [immune-high] SICs [sarcoma immune classes], which are associated with favorable outcomes, providing high infiltration of B cells. The integrative analysis demonstrates that infiltration by B cells is a key discriminative feature of a group of patients with improved survival. This B-cell-high group was found to respond better to PD1 blockade therapy, although this should be validated on a larger cohort," the study states.

"Based on these results, it may now be possible for us to identify more types of sarcomas for which we can use immunotherapy effectively," Tawbi added.

The authors are working to validate these findings in a broader cohort of patients and to identify the underlying mechanisms for B cells acting in tumors. They suggest the findings might be used to build a novel risk-stratification tool for better utilizing immunotherapies in sarcoma patients. ■

EDITCONNECT: E022001

EAGLE

CONTINUED FROM PAGE 12

critical care and disorders that have significant unmet patient needs, such as Alzheimer's disease, the most common form of dementia," stated Scott Tarriff, CEO of Eagle Pharmaceuticals. "Dantrolene sodium's potential for use in treating Alzheimer's patients represents novel thinking backed by years of proprietary Eagle research. Preclinical work around this has proven positive thus far, and builds on Eagle's years of insight gained in multiple clinical and preclinical studies on dantrolene sodium."

Eagle believes that the homeostatic balance of calcium inside cells is essential for the proper function of the nervous system. The company continues to look into how Ryanodex plays a role in restoring intracellular calcium regulation, and its extensive experience with the drug suggests that changes in intracellular calcium levels or calcium signaling, which involve complex cellular pathways, may be involved in neurological pathologies and may lead to neurodegeneration and neuron death.

A proof-of-concept preclinical study conducted at Penn with Eagle's participation was presented in July at the 2019 Alzheimer's Association International Conference, and showed that intranasal dantrolene achieved a greater passage across the blood-brain barrier with higher brain concentrations compared to other routes of administration. Additionally, it showed a disease-modifying effect (improved cognition and memory) and no significant side effects in an animal model of Alzheimer's disease.

Ryanodex is currently approved for the treatment of malignant hyperthermia, which is a life-threatening condition. Eagle's advanced nanosuspension technology is combined with a lyophilized formulation that allows Ryanodex to be reconstituted with sterile water for injection and administered in significantly less time compared to other formulations of dantrolene sodium.

Years of research have lead to the conclusion that calcium dysregulation likely plays a role in Alzheimer's disease as well as an understanding and focus on the drug's role in intracellular calcium regulation. Much of this research focuses on the ryanodine receptor, which is an intracellular calcium channel. Ryanodine receptor dysfunction can lead to excessive calcium release from the endoplasmic reticulum in brain cells, which may trigger a subsequent signaling cascade that induces cell damage and/or cell death. Ryanodex's mechanism of action modulates intracellular calcium release by inhibiting ryanodine receptors in brain cells, and it appears to help restore intracellular calcium homeostasis. Eagle and University of Pennsylvania researchers independently concluded that dantrolene sodium has potential as a disease-modifier for Alzheimer's disease.

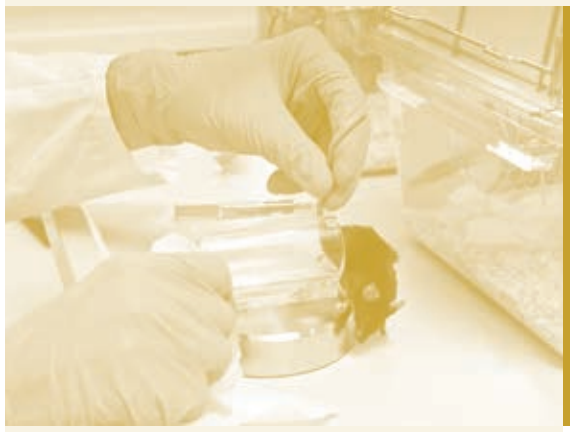
"We are encouraged by the preliminary work we have done together and the potential of dantrolene as a first-in-class treatment option for this devastating disease," said Dr. Huafeng Wei, an associate professor of the Department of Anesthesiology and Critical Care and principal investigator for the animal studies at University of Pennsylvania.

"Our approach—using dantrolene for Alzheimer's disease—is unique," Tarriff tells *DDNews*. "Results from this proof-of-concept preclinical study were presented at the July 2019 Alzheimer's Association International Conference and support the next stages of our collaboration with University of Pennsylvania. We're looking forward to continuing our work with University of Pennsylvania and sharing our results with the public as we progress."

In addition to Alzheimer's disease, Eagle is studying the role of intracellular calcium regulation in brain damage secondary to exertional heat stroke, nerve agent exposure, acute radiation syndrome and traumatic brain injury, which includes concussion. In some cases, this is the first and only research target available at this time. This marks the tenth project currently underway for Eagle, a pharmaceutical company focused on developing and commercializing innovative and differentiated injectable products that address the shortcomings, as identified by physicians, pharmacists and other stakeholders, of existing commercially successful injectable products.

Updates from the JPM Healthcare Conference in San Francisco last month touched on Eagle's growth plan, outlining both the company's financial stability and plans for five additional project launches in the next three years, including targets used for treatment of breast and pancreatic cancers. Moreover, it gave a detailed illustration of how Ryanodex works and the potential it has in treatment under nine different patents expiring between 2022 and 2025. Partnerships on these projects include The United States Army Medical Research Institute of Chemical Defense, NorthShore University HealthSystem and TYME Technologies. ■

EDITCONNECT: E022010



PRECLINICAL

BRIEFS

A global network

GUILDFORD, U.K.—MR Solutions' efforts to expand its support network are continuing apace, with the company announcing that it now has more than 2,000 sites across the globe, with a presence on every continent except Antarctica. The company specializes in offering its base of preclinical liquid helium free multi-modality MRI systems for research laboratories, as well as high field MRI scanners, solid state clip on PET, ringless detectors and a range of state-of-the-art multi-modality CT scanners.

Applications welcome

YEMASSEE, S.C.—As of last month, the Alpha Genesis Primate Research Center, the designated contract research organization of Alpha Genesis Incorporated, is accepting applications for the Alpha Genesis International Research Program. This program is open to investigators globally and is intended to encourage worldwide development of primate models to help advance human and animal medical treatments. Additional information can be requested via info@alphagenesisinc.com.

'Robustly' inhibiting glucocorticoid pathway

SOUTH SAN FRANCISCO, Calif.—ORIC Pharmaceuticals recently presented new preclinical data on ORIC-101, a glucocorticoid receptor (GR) antagonist currently in a Phase 1b clinical trial in combination with nab-paclitaxel in patients with advanced solid tumors. The presentation was at the 2019 San Antonio Breast Cancer Symposium, involving a poster titled "ORIC-101 Robustly Inhibits the Glucocorticoid Pathway and Overcomes Chemoresistance in TNBC." GR is highly expressed in such cancers as prostate, pancreatic, ovarian, triple-negative breast and endometrial. Studies have indicated that activation of GR reduces the efficacy of chemotherapy, while inhibition of GR with the antagonist ORIC-101 enhances the efficacy of chemotherapy in multiple solid tumor models.

IN THIS SECTION

Targeting cancer with Claudin 6

BioNTech announces publication of preclinical data for a CARVac targeting Claudin 6

BY MEL J. YEATES

MAINZ, Germany—BioNTech SE recently announced a publication in *Science* regarding the company's novel CAR-T therapeutic approach for solid tumors. The article, entitled "An RNA vaccine drives expansion and efficacy of claudin-CAR-T cells against solid tumors," provides preclinical proof-of-concept data for BioNTech's first CAR-T product candidate: BNT211, an autologous CAR-T cell therapy targeting the oncofetal antigen Claudin 6. The study also outlines CARVac as a broadly applicable RNA vaccine approach to improve the therapeutic efficacy of CAR-T cell therapies.

According to Sean Marett, chief business and chief commercial officer for BioNTech, "BNT211 is CAR-T cell therapy targeting a new solid tumor antigen (Claudin 6, also CLDN6) that is combined with an

BIONTECH CONTINUED ON PAGE 17

CREDIT: BIONTECH

In a recently published study, BNT211 was evaluated both *in vitro* in tumor cell lines and *in vivo* in mice with human ovarian cancer transplants. The CLDN6-CAR-T cell therapy demonstrated complete tumor regression of transplanted large human tumors within two weeks after initiation of treatment.

Activating innate immunity against breast cancer

Silverback Therapeutics' SBT6050 shows promise in HER2-expressing tumors

BY KRISTEN SMITH

SEATTLE—The latest news to emerge from biopharmaceutical company Silverback Therapeutics seems to reinforce the promise of SBT6050, their anti-HER2 antibody conjugated to a potent TLR8 agonist, for treatment of moderate and high HER2-expressing tumors.

Silverback issued periodic positive updates throughout 2019, indicating SBT6050's ability to drive activation of both innate and adaptive immune responses, resulting in single-agent efficacy in mouse models. Working as a TLR8 agonist conjugated to a HER2-directed monoclonal antibody, SBT6050 seems to activate myeloid cells only in the presence of HER2-expressing tumor cells with moderate-to-high expression levels. Due to localized activation of myeloid cells,

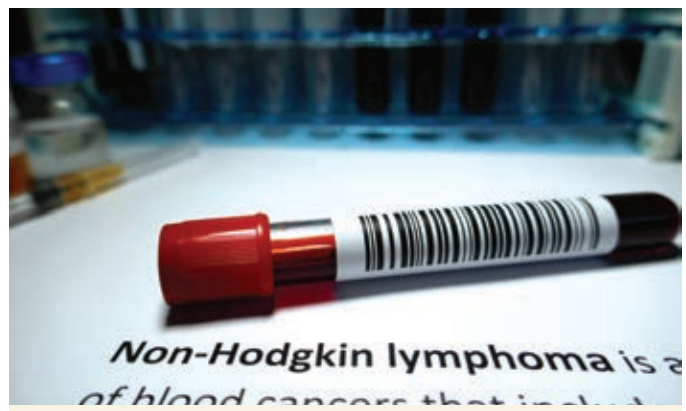
SILVERBACK CONTINUED ON PAGE 18

SILVERBACK THERAPEUTICS

Preclinical data indicate that Silverback Therapeutics' SBT6050 may be useful as a single-agent therapeutic or in combination with trastuzumab-based therapies, providing a much-needed immunotherapeutic option for patients with HER2-expressing disease.

TLR conjugates do not cause an overproduction of peripheral cytokines in preclinical models, thus minimizing cytotoxicity found in other approaches to these tumors.

"TLR8 activation of tumor-resident myeloid cells results in potent antitumor immune responses, but effective delivery has been the key challenge," said Dr. Valerie Odegard, Silverback's chief scientific officer. "Our



Preclinical studies investigating the effect of Betalutin on non-Hodgkin's lymphoma (NHL) cell lines appear to demonstrate that the drug, as part of a combination regimen, could be an effective therapy for NHL.

Reversing resistance

Drug can affect non-Hodgkin's lymphoma cell lines

BY ILENE SCHNEIDER

OSLO, Norway—Non-Hodgkin's lymphoma (NHL) is an indication with substantial unmet medical need, with a growing market forecast to be worth nearly $29 billion by 2026. Preclinical studies investigating the effect of Betalutin (177Lu-lilotomab satetraxetan) on NHL cell lines appear to demonstrate that the drug, as part of a combination regimen, could provide effective therapy for NHL. Nordic Nanovector is attempting

NORDIC CONTINUED ON PAGE 17

BIONTECH

CONTINUED FROM PAGE 16

accompanying mRNA-vaccine, called CARVac (CAR-T cell Amplifying RNA Vaccine). Our preclinical studies demonstrate that [therapeutic] challenges may be addressed by the additional application of the CARVac that encodes the CAR-T target, in this case CLDN6. By the additional body-wide presentation of the CAR-T target, the CAR-T cell population is re-stimulated leading to enhanced engraftment, proliferation and tumor infiltration rates."

Although CAR-T cell therapy has shown significant clinical efficacy in blood cancers, it faces challenges in solid tumors, including a limited number of identified cancer-specific solid tumor targets, inefficient infiltration of CAR-T cells into solid tumors, and insufficient CAR-T cell persistence. BioNTech aims to overcome these hurdles.

"BNT211 was created as part of our CAR-T pipeline that uses tailored reprogramming of autologous T cells from cancer patients to recognize and address their tumors," notes Marett. "A key hurdle for CAR-T therapy in solid tumors is the very limited number of validated CAR-antigens that are exclusively expressed on solid tumors. CLDN6 is a protein active in embryogenesis that is silenced in healthy cells during life, but specifically expressed in a variety of solid tumors."

"Claudin 6 is a tight junction membrane protein which in normal tissue is solely expressed in embryonic cells, but is aberrantly expressed by a number of solid tumors such as uterine, testicular, ovarian and lung cancer. In preclinical tests of our CAR-T therapy directed against Claudin 6, we observed potent antitumoral efficacy, including eradication of advanced tumors in an ovarian carcinoma xenograft model," he continues. "Furthermore, we did not observe any cross-reactivity with closely related CLDN-proteins or side effects in healthy tissues, underlining its specificity.

"To further improve therapeutic impact, we are combining the CAR-T therapy with another of our proprietary platforms—our CARVac approach, which is based on our longstanding mRNA expertise. With our proprietary RNA-Lipoplex formulation, we can successfully deliver antigen-encoding mRNAs via IV application to lymphoid compartment resident antigen-presenting cells in the whole body promoting priming and strong expansion of antigen-specific (CAR)-T cells."

In the published study, BNT211 was evaluated both *in vitro* in tumor cell lines and *in vivo* in mice with human ovarian cancer transplants. In mice, the CLDN6-CAR-T cell therapy demonstrated complete tumor regression of transplanted large human tumors within two weeks after initiation of treatment. The combination with CARVac achieved an improved engraftment, proliferation and expansion of CAR-T cells *in vivo*, resulting in tumor regression even at subtherapeutic CAR-T doses.

CARVac was also successfully applied for CAR-T cells targeting the pan-cancer antigen CLDN18.2 and CD19, the target of approved CAR-T cell therapies. BioNTech believes that the combination of CAR-T cell therapy with CARVac underlines the value of cross-platform synergies in addressing development challenges in cancer treatment.

CREDIT: BIONTECH

"BNT211 was created as part of our CAR-T pipeline that uses tailored reprogramming of autologous T cells from cancer patients to recognize and address their tumors," says Sean Marett, chief business and chief commercial officer for BioNTech. "A key hurdle for CAR-T therapy in solid tumors is the very limited number of validated CAR-antigens that are exclusively expressed on solid tumors."

BioNTech plans to initiate a first-in-human Phase 1/2 clinical trial for validation of safety and efficacy of BNT211 in solid tumors—including ovarian, testicular, uterine and lung cancer—in the first half of 2020.

"There are two key challenges to using CAR-T therapies in solid tumors; solid tumor specificity and maintaining fit, active CAR-T cells that can attack and destroy tumor cells," explains Marett. "Our first CAR-T candidate directed against CLDN6 in combination with our CARVac approach potentially may address both of these challenges, as evidenced by our preclinical data that we published recently in *Science*, leading us to prepare for clinical testing of our first CAR-T in combination with CARVac this year."

He also says that "a great advantage of our mRNA-based CARVac technology is that it can easily be adapted to other CAR-T cell targets, and thus is potentially widely applicable—offering a broad potential to improve therapeutic efficacy of CAR-T cell therapies across a range of solid and liquid tumors, heralding a potentially new way of treating tumors with CAR-T cell therapies. In addition, our combination of CAR-T cell therapy with an mRNA therapeutic vaccine directed against the same target highlights the value of cross-platform synergies at BioNTech to address key development challenges in the treatment of cancer."

"We plan to initiate a first-in-human Phase 1/2 clinical trial for validation of safety and efficacy of BNT211 in solid tumors, including ovarian, testicular, uterine and lung cancer, in the first half of 2020. It's exciting to make progress in the challenging field of CAR-T therapy in solid tumors," Marett tells *DDNews*.

Manufacturing to support clinical trials of BNT211 will be conducted at BioNTech's state-of-the-art GMP-certified cell therapy manufacturing facility in Idar-Oberstein, Germany, which has been in operation since 1999. BioNTech initiated a multi-year capacity expansion at the facility in 2018, which the company expects to complete sometime in 2020. ■

EDITCONNECT: E022012

NORDIC

CONTINUED FROM PAGE 16

to commercialize Betalutin in core markets.

Nordic Nanovector, which presented a poster at the 61st American Society of Hematology (ASH) Annual Meeting & Exposition in December 2019 in Orlando, has been conducting a research program to investigate resistance mechanisms that enable NHL cells to survive Betalutin treatment and to identify molecules that, when used in combination with Betalutin, could overcome that resistance. The outcome of this research could have an impact on future programs designed to expand the use of Betalutin-based therapies in NHL patients.

According to Nordic Nanovector, a company that develops targeted therapies for hematological cancers, the research presented at ASH built on data presented at the European Hematology Association annual meeting in June 2018. That research demonstrated how a screen of more than 50 different NHL cell lines identified some cell lines that were resistant to Betalutin.

The ASH poster showed how these two aggressive diffuse large B cell lymphoma (DLBCL) cell lines have been used in a new screen where Betalutin has been combined with 384 different anticancer drugs to identify the Betalutin/drug combinations that could potentially contribute to reverting resistance. The CD37 targeting radioimmunoconjugate 177Lu-lilotomab satetraxetan (Betalutin) is currently being evaluated as monotherapy in a clinical Phase 2b trial for patients with follicular lymphoma (FL), in a Phase 1 trial for patients with DLBCL, as well as in a Phase 1b trial in combination with rituximab for patients with relapsed/refractory FL.

"Our ongoing research programs and collaborations continue to help us understand how NHL cells react to Betalutin treatment. Understanding the mechanisms of resistance to Betalutin, and how to overcome them, is crucial for being able to deliver optimal treatment to patients with difficult-to-treat tumors."
Jostein Dahle, chief scientific officer of Nordic Nanovector

Nordic Nanovector investigated the effect of 177Lu-lilotomab satetraxetan in seven activated B-cell like (ABC) DLBCL cell lines. While the radioimmunoconjugate showed anti-tumor activity, primary resistance was observed in a subset of cell lines: U-2932 and RIVA. Both cell lines are representative for TP53 deficient double expressor (DE) DLBCL. Importantly, resistance was not a consequence of reduced binding of the radioimmunoconjugate to cell surface expressed CD37. Armed with this knowledge, Nordic Nanovector set out to identify drugs able to overcome the resistance to 177Lu-lilotomab satetraxetan in both resistant ABC-DLBCL cell lines.

As Jostein Dahle, chief scientific officer of Nordic Nanovector, explained, "Our ongoing research programs and collaborations continue to help us understand how NHL cells react to Betalutin treatment. Understanding the mechanisms of resistance to Betalutin, and how to overcome them, is crucial for being able to deliver optimal treatment to patients with difficult-to-treat tumors. In the case of Betalutin-based treatment, which to date has demonstrated an encouraging clinical profile, such combination strategies could further enhance its potential to become an important option for NHL patients."

In other news, Nordic Nanovector's research and development project Nanoyield received a non-dilutive funding of NOK12 million ($1.3 million) from the Norwegian Research Council (Forskningsrådet). The Nanoyield project is targeted at optimizing the production yield of Nordic Nanovector's CD37-targeting antibody NNV003, the antibody component of the radioimmunoconjugate Alpha37. The project will be conducted in partnership with SINTEF Biotechnology, one of Europe's largest independent research institutes.

Additionally, Nordic Nanovector received grant funding of €600,000 from Eurostars, a European R&D funding program, to advance the Alpha37 program. Alpha37 comprises NNV003 with the alpha-particle generator lead-212 (212Pb) and is being advanced in an R&D collaboration with Orano Med. Preclinical data presented at international cancer congresses during the past year have indicated that a single injection of Alpha37 is well tolerated and produces a promising anti-cancer effect and subsequent improvement on survival in preclinical models of CD37-positive chronic lymphocytic leukemia (CLL) and NHL.

Dahle summarized, "We are excited to receive this new non-dilutive grant funding from Forskningsrådet to advance the Alpha37 program. Alpha-emitting radionuclides have demonstrated good potential for targeted cancer therapies. Their high energy is limited to a few cell widths, resulting in localized cytotoxicity while sparing surrounding healthy tissues. We have seen very encouraging preclinical evidence demonstrating the potential of Alpha37 to treat CLL and NHL, and with our partners are advancing this exciting candidate towards clinical trials in these indications." ■

EDITCONNECT: E022014

Transgene and BioInvent announce data for BT-001 in solid tumors

Broad antitumor activity shown in immunocompetent models sensitive or resistant to immune checkpoint blockade

BY *DDNEWS* STAFF

STRASBOURG, France & LUND, Sweden—Toward the end of 2019, Transgene, a biotech company that designs and develops virus-based immunotherapeutics against cancer, and BioInvent International AB, a biotech company focused on the discovery and development of novel and first-in-class immunomodulatory antibodies for cancer immunotherapy, announced "compelling results" from extensive *in-vitro* and *in-vivo* preclinical studies with BT-001.

BT-001's therapeutic activity was assessed in several immunocompetent preclinical mouse models, showing "outstanding antitumoral activity for BT-001 murine surrogate antibody-encoding viruses conferring cures in a majority of mice transplanted with different solid cancer tumors."

The therapeutic being co-developed by Transgene and BioInvent is an oncolytic virus (OV) expressing an anti-CTLA4 antibody and the cytokine GM-CSF—a multifunctional OV. It was generated using Transgene's Invir.IO platform and its patented large capacity VVcopTK-RR- oncolytic virus, which has been designed to encode for a Treg-depleting anti-CTLA4 antibody derived from BioInvent's proprietary n-CoDeR/F.I.R.S.T platforms as well as the cytokine GM-CSF.

The therapeutic activity was assessed in several immunocompetent preclinical models, reportedly showing outstanding antitumoral activity for BT-001 murine surrogate antibody-encoding viruses conferring cures in a majority of mice transplanted with different solid cancer tumors—more than 70 percent in all tested models, according to the companies.

The new preclinical data also confirmed that the anti-CTLA4 antibody expressed by BT-001 in mouse tumor cells retained biochemical integrity and folding, functionality and biological activity. Moreover, BT-001's biodistribution profile is said to have demonstrated higher concentration and prolonged activity of the anti-CTLA4 antibodies in tumors compared to intravenous anti-CTLA4 antibody therapy.

"Thanks to the fruitful collaboration between Transgene and BioInvent, we have been able to generate these exciting preclinical data with BT-001. We have confirmed that BT-001 is able to replicate within cancer cells in immunocompetent models, and locally produce high and long-lasting concentrations of both anti-CTLA4 antibody and GM-CSF, leading to the destruction of the tumor," said Dr. Éric Quéméneur, executive vice president and chief scientific officer at Transgene. "Based on these data, we are optimistic that upcoming clinical trials with BT-001 will deliver improved efficacy while minimizing the adverse events that have been associated with this class of immune checkpoint inhibitor."

BioInvent and Transgene both confirm that they intend to submit a clinical trial application in the first half of 2020 to conduct a first-in-human trial with BT-001 in Europe and in the United States.

"With BT-001, we build on the success of three clinically validated axes of activating patients' own immune defense to combat cancer: anti-CTLA-4, anti-PD-1/PD-L1 and oncoviral immunotherapy. We are excited to bring forward to clinical testing our antibody-encoding oncolytic virus, which has indicated synergistic activity and potential for significantly improved tolerability compared to available anti-PD-1/anti-CTLA-4 combination therapy" said Dr. Björn Frendéus, chief scientific officer of BioInvent. ■

EDITCONNECT: E022015

SILVERBACK

CONTINUED FROM PAGE 16

preclinical studies demonstrate that systemic delivery of a TLR agonist with tumor-localized activity dramatically rewires the tumor microenvironment, resulting in durable, single-agent efficacy in tumors refractory to checkpoint blockade."

According to Dr. Peter Thompson, Silverback's co-founder, chairman and CEO, what led the company to explore the innate immunity offered by myeloids was the intent to take the known potent tumor agonist TLR8 and identify a way to apply it locally. SBT6050 is Silverback's novel immune-modulatory conjugate that utilizes cell surface expression of HER2 to localize activation of TLR8 (toll-like receptor 8) for the treatment of HER2-expressing tumors, delivering a heavy immune payload distinct from the cytotoxicity found by activating T cells and lymphocytes.

"Our data show the successful, specific delivery of a TLR agonist to HER2-expressing tumor cells upon systemic administration—thereby addressing a fundamental challenge previously limiting use of innate immune agonists to topical and intratumoral administration, largely due to toxicity arising from widespread myeloid cell activation with systemic use of these agents," stated Thompson. "Unlike other innate immune agonists that have been limited to topical or intratumoral administration, SBT6050 is designed for systemic delivery and tumor-localized activity. With this validating data in hand, we are applying our technology to a broad range of targets and diseases."

"TLR8 activation of tumor-resident myeloid cells results in potent antitumor immune responses, but effective delivery has been the key challenge. Our preclinical studies demonstrate that systemic delivery of a TLR agonist with tumor-localized activity dramatically rewires the tumor microenvironment, resulting in durable, single-agent efficacy in tumors refractory to checkpoint blockade."

Dr. Valerie Odegard, chief scientific officer of Silverback Therapeutics

CREDIT: SILVERBACK THERAPEUTICS

"Our data show the successful, specific delivery of a TLR agonist to HER2-expressing tumor cells upon systemic administration—thereby addressing a fundamental challenge previously limiting use of innate immune agonists to topical and intratumoral administration, largely due to toxicity arising from widespread myeloid cell activation with systemic use of these agents," says Dr. Peter Thompson, CEO of Silverback.

What is most exciting to Thompson is the ability to utilize the more primitive element of the immune mechanism even in patients showing no signs of an intact adaptive immune response to a tumor. He explained that they specifically wanted to look at those patients who showed no functioning T cell response to test how effective the innate immune response of just the myeloid systems could be. Because tumors are not heterogenic and differ from site to site, they were also hoping to find a composition class that could be activated systemically rather than locally. Likewise, they sought an agent that did not react to normal, heathy tissue that features small amounts of HER2 or HER3 expression. In all facets, SBT6050 is showing very promising results.

"SBT6050's ability to drive a broad spectrum of antitumor immune responses through localized and potent activation of human myeloid cells has not been achieved by other cancer immunotherapies," Odegard remarked. "Our preclinical data continue to highlight the potential for single-agent clinical activity with SBT6050, even in settings with diminished or absent T cell infiltrates, and now demonstrate the opportunity for enhanced activity in combination with trastuzumab. We are excited to rapidly advance SBT6050 into the clinic."

Dr. Naomi Hunder, Silverback's senior vice president of clinical development, added "Despite advances in treatment options for patients with HER2-expressing tumors, significant unmet medical need remains, and immune checkpoint inhibitors have demonstrated activity in only a subset of these patients. Preclinical data indicate SBT6050 may be useful as a single-agent therapeutic or in combination with trastuzumab-based therapies, providing a much-needed immunotherapeutic option for patients with HER2-expressing disease. We plan to initiate clinical investigation of SBT6050 in 2020." ■

EDITCONNECT: E022013

Prospects for global ADME-Tox: High need but potential roadblocks

MOUNTAIN VIEW, Calif.—According to the report "Global ADME-Tox Screening Systems dynamics comprehensive analysis business growth prospects and opportunities 2025" from QY Research, North America is expected to dominate the ADME-Tox screening system market due to the presence of a large number of biopharmaceutical companies in this region.

FOCUS FEATURE: TOX SCREENING

"The increasing focus of drug manufacturers to reduce the development cost of drug with least toxicological issue is the major factor driving the growth of ADME-Tox screening system market."
QY Research

The European and Asia-Pacific regions come after North America for the ADME-Tox screening system market. In the Asia-Pacific region, India and China are expected to be the fastest-growing market over the forecast period, owing to increased focus by leading biopharmaceutical manufacturers to expand their subsidiaries in these countries.

The increasing focus of drug manufacturers to reduce the development cost of drug with least toxicological issue is the major factor driving the growth of ADME-Tox screening system market, as reliable and accurate ADME-Tox testing increases the potential of a drug by increasing the efficiency of the drug to target the desired tissue.

Moreover, increasing demand for specialized drugs due to rising prevalence of various chronic diseases will also boost the growth of the ADME-Tox screening system market, says QY Research. High installation and maintenance cost of such systems, though, could hamper growth, and a lack of skilled professionals to operate such systems could contribute to sluggish growth in this market.

ADME-Tox screening involves an integrated workstation for describing of the absorption, distribution, metabolism and excretion (ADME) properties of drug molecules. ADME-Tox screening systems include a biochemical assay tester that measures the physicochemical properties of a drug molecule. This system also supports the permeability assays testing, which measures the drug's affinity toward metabolic enzyme.

ADME-Tox screening systems are enabled with highly integrated software that has an inbuilt protocol for the sample testing. The protocol feed in the software can be edited as per the customized need of sample testing. ADME-Tox screening systems also are connected to a multi-mode reader which allows runs the wide range of protocol on primary and secondary screen. The system thus provides accurate toxicity tests for drug development and biopharmaceutical production. ■

EDITCONNECT: E022035

Q&A: Transgenic rasH2 mice and the 3Rs are transforming drug safety testing

BY *DDNEWS* STAFF

BESIDES THE TYPICAL DRUG DISCOVERY constraints of time and money, when it comes to drug safety screening there is usually a desire to use fewer animals in keeping with Russell & Burch's 3Rs (replacement, reduction and refinement) philosophy. Being able to conduct the required drug safety screening in less time, with fewer animals and at a lower cost, can be a significant advantage.

According to Taconic Biosciences Inc., the transgenic rasH2 mouse model is transforming ADME-Tox testing by replacing the traditional two-year carcinogenic assessment with a 26-week study that uses fewer animals. The potential utility of this model also extends to new applications, including an eight-week dermal carcinogenic risk assessment that can be utilized prior to laborious, time-consuming regulatory studies.

Additionally, a few new studies are showing rasH2 in combination with error-corrected, next-generation sequencing (EC-NGS) as a predictive tumorigenic assay that can be utilized in a one-month study and implemented much earlier in the drug development process. *DDNews* recently spoke with Terry Receveur, associate director of product management at Taconic Biosciences, about how the rasH2 model is enhancing drug safety testing.

CREDIT: TACONIC BIOSCIENCES

"There is strong evidence in emerging research for using rasH2 with EC-NGS as a predictive tumorigenic assay that can be utilized in a one-month study and implemented much earlier in the drug development process."

Terry Receveur of Taconic Biosciences

DDNEWS: **What is a rasH2 mouse?**

Terry Receveur: The rasH2 mouse was developed in the laboratory of Tatsuji Nomura of the Central Institute for Experimental Animals (CIEA) in Kawaski, Japan. The rasH2 mice carry the human c-Ha-ras oncogene in addition to the endogenous murine Ha-ras oncogene. The presence of the human c-Ha-ras gene makes hemizygous rasH2 mice highly susceptible to tumor development when exposed to compounds that cause cancer in humans.

DDNEWS: **Why has the industry adopted the use of the rasH2 for carcinogenicity studies so readily?**

Receveur: Compared to the traditional two-year study, the rasH2 model provides a more accurate and faster result that is regulatory approved and accepted, at a lower cost. Companies looking to comply with Russell & Burch's 3Rs also find the rasH2 model aligns well.

The six-month rasH2 carcinogenicity study is approved by The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) and the FDA as a substitute for the traditional two-year rodent carcinogenicity studies. It reduces the in-life testing timeline by 75 percent, has extremely low incidence of spontaneous tumors, and provides more rapid onset and higher incidence of more malignant tumors.

Using only 25/sex/group (versus 50 to 60) means less test article required and a huge decrease in post-study pathology. The rasH2 also has a robust historical control database to support decisions on carcinogenicity susceptibility, displays low mortality, shows no drift in tumor incidence, and experiences stable body weight data among groups. Over 75 percent of mouse carcinogenicity studies are now conducted in the rasH2.

DDNEWS: **How does the rasH2 support Russell & Burch's 3Rs?**

Receveur: Russell and Burch originated the concepts of replacement, reduction and refinement (3Rs) in their 1959 book, *The Principles of Humane Experimental Technique (Principles)*, proposing a new applied science to improve treatment of laboratory animals and advance the quality of science in studies that use animals. The 3Rs were put forward to help investigators find and use available techniques and encourage developing new tools and methodologies.

The rasH2 model applies to two of the Rs. By using only 25/sex/group, the number of animals per study is reduced by 250 to 300 (a more than 50-percent reduction). Use of the rasH2 also considerably reduces the number of mice euthanized due to senescence-related morbidity typically found near the end of two-year studies. The number of repeat studies needed due to inconclusive evidence related to false positives that result from spontaneous tumors is considerably reduced, reflecting refinement in animal use.

DDNEWS: **How is the rasH2 mouse continuing to transform drug safety testing?**

Receveur: Three initiatives underway involving the rasH2 can benefit drug safety testing and drug discovery.

In 2011, Dr. Frank Sistare and colleagues posited that researchers could retrospectively analyze two-year rat bioassay data and, in tandem with six-month rasH2 carcinogenicity studies, predict negative outcomes of two-year rat studies with 80-percent accuracy. They estimated that use of such predictions could reduce the number of required two-year rat carcinogenicity studies by 40 to 50 percent without additional risk to human safety. The ICH's extensive efforts to validate the theory has shown a two-year rat carcinogenicity study provides little value if a compound lacks histopathological risk factors for neoplasia in chronic toxicity studies, does not cause hormonal perturbation, and is negative for genotoxicity. ICH S1 Guidelines are expected to undergo a revision that would allow waiving the requirement for a two-year rat bioassay under certain conditions. The proposed changes could take effect by late 2021. The impact to the 3Rs is significant: fewer animals used, for a shorter time.

Second, a recent article ("Establishment and Validation of an Ultra-Short-Term Skin Carcinogenicity Bioassay Using Tg-rasH2 Mice") confirmed the effectiveness of rasH2 in predicting skin carcinogenicity. This is a follow-up to a 2013 paper ("Tumor Promotion by 12-O-tetradecanoylphorbol-13-acetate in an Ultra-Short-Term Skin Carcinogenesis Bioassay Using rasH2 Mice"), which concluded that skin promotion effects could be detected in only eight weeks in rasH2 mice. This paper validates the rasH2 carcinogenicity bioassay as a tool for assessing the carcinogenicity potential of topically applied chemicals. This new assay reduces the time animals are on study and may replace the use of more sentient species.

Third, there is strong evidence in emerging research for using rasH2 with EC-NGS as a predictive tumorigenic assay that can be utilized in a one-month study and implemented much earlier in the drug development process. Though in the early stages of development and validation, there is compelling information to support its use.

This approach could enable testing for genotoxic and non-genotoxic carcinogenicity in just four weeks. It also adds predictive utility in the drug discovery pipeline in a pre-IND application, allowing organizations to de-risk earlier in the process, saving time and money and enabling screening of more potential life-saving compounds. The assay results also identify mutations in both the murine and human ras gene/transgene without the need for pathology. With this approach, animals are on study for less time, and since compounds that may have caused tumors in the traditional carcinogenicity testing scenario are eliminated, there may be less pain or distress. ■

"Compared to the traditional two-year study, the rasH2 model provides a more accurate and faster result that is regulatory approved and accepted, at a lower cost," says Terry Receveur, associate director of product management at Taconic Biosciences. "Companies looking to comply with Russell & Burch's 3Rs also find the rasH2 model aligns well."

Terry Receveur is the associate director of product management at Taconic Biosciences Inc. He has been in the laboratory animal industry for over 30 years and has held positions in animal production, vivarium management and operational excellence.

SOT/ToxExpo 2020 Show Preview: A taste of toxicology

WHEN IT COMES around, March will bring with it the 59th Society of Toxicology (SOT) Annual Meeting and ToxExpo, held this year in Anaheim, Calif. The meeting is expected to include over 6,000 scientists from countries all over the world. *DDNews* spoke with Ronald N. Hines, SOT president 2019-2020, and George Daston, SOT vice president 2019-2020, to learn what the meeting has in store for its attendees.

"The SOT Annual Meeting is a place where people showcase the best in toxicological research while also sowing the seeds for future research and collaborations."
Ronald N. Hines, SOT president 2019-2020

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

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

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

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

The meeting will take place from March 15-19. For more details, visit www.toxicology.org or use the "search our archives" field at the top of our *DDNews* home page at www.ddn-news.com to look for the code **E012036** and read our show preview feature for SOT/ToxExpo 2020. ■

analytica

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AIMING FOR EXCELLENCE IN ANALYSIS

Science meets industry at the biennial Analytica conference

BY MEL J. YEATES

MUNICH—The very end of March and beginning of April will bring the Analytica conference, held in Munich. A conference organized by Forum Analytik, an alliance of Gesellschaft Deutscher Chemiker (GDCh), Gesellschaft für Biochemie und Molekularbiologie (GBM) and the Deutsche Gesellschaft für Klinische Chemie und Laboratoriumsmedizin (DGKL), Analytica offers a multidisciplinary scientific program that brings users, manufacturers and researchers together and promotes the transfer of knowledge and the exchange of ideas.

"There is more than one reason not to miss Analytica 2020—Analytica is the world's leading trade fair for laboratory technology, analysis and biotechnology," says Susanne Grödl, exhibition director of Analytica. "The accompanying Analytica conference bridges the gap between research and routine analysis. Analytica presents the entire value chain of the laboratory world—with innovations from analysis and quality control, biotechnology, life sciences and diagnostics—and [has] 1200 exhibitors from all over the world (half from Germany)."

The speakers at the Analytica conference are renowned scientists and specialists from all over the world. They report on current topics in analytics, quality control, diagnostics, measurement and testing technology, as well as biotechnology and life sciences. The lectures give an overview of novel methods, procedures, techniques and their application possibilities. Young scientists present the results of their research and innovative applications at the highlight poster show, and attendees are invited to participate in the onsite discussions.

"Analytica is the leading stage for current and future innovations. Major market leaders showcase their international and/or European premieres at Analytica in Munich. Test novelties from laboratory technology and visit the practice-oriented supporting program," adds Grödl. "We offer forums, live labs and 'explosive' demonstrations on workplace health and safety, plus exciting presentations at the 'Personalized Medicine' theme day and, for startups, at the 'Finance' theme days. The special exhibition 'Digital Transformation' is unique worldwide—never before has the digital transformation in everyday laboratory practice been portrayed in such a comprehensive and practically oriented manner."

As Grödl tells *DDNews*, "The megatrends of digitalization and networking are keeping the industry occupied. Hence, we are expanding the Digital Transformation Forum in terms of both space and contents. In addition to keynote speeches, there will be a special show in Hall B2. Industry giants, medium-sized companies and start-ups will be presenting their concepts for the digital transformation live here."

"The Digital Transformation Forum will offer direct know-how transfer with the latest solutions for the world of tomorrow. Participants will attend presentations and discussions with renowned experts on topics, such as: What will the laboratory of the future be like (short, thought-provoking presentations)? Benefits of digital networking (interfaces /LIMS). What does this mean for manufacturers and users? How can I make my laboratory even more efficient? How can laboratory processes be optimized? How can I manage data diversity and, notably, data security? How can regulations and standards

ALL IMAGES PROVIDED BY FORUM ANALYTIK. CONFERENCE PHOTOS ARE FROM PREVIOUS ANALYTICA MEETING IN 2018 (CREDIT: THOMAS PLETTENBERG, MESSE MÜNCHEN GMBH). USE OF ANALYTICA LOGO AND PHOTOS DOES NOT CONSTITUTE ENDORSEMENT OR SPONSROSHIP OF THIS PRE-SHOW COVERAGE BY FORUM ANALYTIK.

be implemented ideally? [And] new developments from the fields of automation and robotics," she notes.

"Walking through the exhibition halls, it is apparent that digitalization has been embraced by all analytical disciplines. The health sector benefits particularly from this. In the areas of image analysis—such as analysis of X-ray images or tissue sections—artificial intelligence is clearly superior to the human brain," states Grödl. "In the field of oncology, automated pattern recognition enables a more accurate identification of tumors and metastases, and the course of disease can be monitored more effectively."

"Digitalization also allows various diagnostic instruments, such as those for genome and proteome analysis or computed tomography, to be linked and connected with databases. Intelligent software assists physicians with the interpretation. The goal is to understand the pathogenic mechanisms and the modes of action of drugs even better," she continues. "Future therapies should focus more on the patient's individual pathology, as this is the only way to increase therapeutic success and reduce side effects. On April 3, Analytica [will devote] a theme day to personalized medicine at the Biotech Forum in Hall A3.

"[Analytica] covers the entire spectrum of modern analytics and invites you to look beyond your own specialist boundaries. Those who engage in this will discover synergetic effects. Artificial intelligence technology, for example, not only helps in the evaluation of X-ray images in the medical field, but also in material analysis and quality control. Likewise, DNA analyses can be used not only to recognize diseases or identify people, but also to verify the authenticity of foods."

Grödl tells *DDNews* that Analytica creates an ideal setting for collaborations between manufacturers and their clients: "Most analytical systems can be used in a variety of ways, but must be adapted to the respective measurement task. Manufacturers modify their devices accordingly and develop specific measurement protocols and data analysis software. They also work closely with users from science and industry to ensure that the systems meet the customer's specific needs. The unique combination of the world's leading trade fair, scientific conference and the varied framework program offers suppliers and users from all over the world plenty of opportunity for the exchange of ideas and know-how."

She says that one highlight is an "Action Area" that will demonstrate automated workflow using concrete examples, noting that it will "make the special exhibition globally unique. The centerpiece of the exhibition is a robotic arm demonstrating human-machine collaboration that can be used, among other things, in DNA extraction. Fair visitors can try out process steps for themselves at six hands-on exhibition stands, including sample preparation, intelligent sample logistics, assisted execution of a protocol and optical analysis. Using the example of a networked bioreactor, it becomes clear how digital technologies invariably help to optimize processes. A virtual reality area and the use of a digital laboratory journal provide insight into the laboratory processes of tomorrow and beyond."

Grödl specifies that the Analytica conference has over 200 lectures to bridge the gap between research and routine analysis, and highlights for *DDNews* readers a series of lectures on March 31 that will focus on biotechnologically produced active pharmaceutical ingredients.

"The importance of analysis for the pharmaceutical and healthcare sector pervades the entire Analytica conference. On March 31, sessions on medical informatics and clinical mass spectrometry are on the agenda, and on April 1, the program continues with reference intervals in endocrinology and detection of antibiotic-resistant bacteria and other pathogens," she continues. "On April 2, liquid biopsies for personalized cancer medicine will move into the focus. This still relatively new technique can be used to detect cancer cells or tumor DNA in the blood."

No other event informs as comprehensively about the entire gamut of chemical and bioanalytical examination methods as the Analytica conference, according to Grödl, who adds, "The multifaceted program … invites you to look beyond your own horizons and let yourself be inspired by colleagues from other analytical disciplines."

Looking at other highlights of the Analytica conference, Grödl notes that during the first two days of the fair, the Biotech Forum in Hall A3 will offer expert lectures on innovative products in the fields of life science and biotechnology, with topics such as next-generation sequencing and the latest practical tips on instrumental analytics.

"At the 'Personalized Medicine' theme day, experts from biotechnology, pharmaceutical and IT-diagnostic companies, associations and clusters will discuss the current state and future directions of personalized medicine," she continues. "Why does digitization play such an important role in this area, too? Why does the much-advertised digital medical record only help to a limited extent here, and how can the difficult to calculate costs be covered? On the last day of the fair, from 10 a.m. to 3 p.m., exciting lectures and discussion rounds will highlight the topic from a variety of perspectives and enable everyone to form a comprehensive opinion."

"Analytica is the world's leading trade fair for laboratory technology, analysis and biotechnology. The accompanying Analytica conference bridges the gap between research and routine analysis [and] presents the entire value chain of the laboratory world."

Susanne Grödl, exhibition director of Analytica

As for what may be in store for next time, "The next [Analytica meeting] will take place in 2022. We currently expect that the topic of digitalization will continue to play a major role in the laboratory, certainly also in conjunction with the topic of sustainability," Grödl concludes. "Which focus we set [for a meeting] is usually decided one-and-a-half years before the next trade fair. We then pick up on current and future challenges and developments with new concepts and formats, and exhibit these at the fair." ■

EDITCONNECT: E022036

ANALYTICA AWARDS

Bunsen Kirchhoff Award

The Bunsen-Kirchhoff Award is dedicated mainly to young scientists for extraordinary contributions in the field of spectroscopy. It is awarded by the German Working Group for Analytical Spectroscopy (DAAS) in the GDCh Division Analytical Chemistry. The prize, endowed with €3,000 by Analytik Jena AG, is to be presented at the Analytica conference 2020 in Munich on April 2.

Eberhard Gerstel Award

The Eberhard Gerstel prize was awarded for the first time in 2010, by the Separation Science working group in the GDCh Division Analytical Chemistry, for an outstanding publication in the field of analytical separation techniques. The biennial prize of €2,000 is donated by GERSTEL GmbH & Co. KG Mülheim an der Ruhr.
The Eberhard Gerstel Prize will be awarded as part of Analytica 2020.

Application Award and Start Up Award

The newest laboratory equipment or the most sensitive analytical instrument is only one aspect of a successful analysis. Often the right method or application brings the optimal result. To reflect this, LABORPRAXIS is awarding the Application Award again during Analytica 2020. The award looks for the most exciting application in four categories: laboratory technology, biotechnology & pharmaceutical, water & environment, and food analysis. And new in 2020 is the special category "Digital Laboratory." Applications are open until February 29.

ANALYTICA CONFERENCE AGENDA: SESSIONS AND CHAIRS

TUESDAY, MARCH 31

Biopharmaceuticals I—From Molecules to Therapy
Dr. Anne Arnold, Immundiagnostik AG, Bensheim
Dr. Roland Kellner, Merck KGaA, Darmstadt

Biopharmaceuticals II—From Concepts to Products
Dr. Anne Arnold, Immundiagnostik AG, Bensheim
Dr. Roland Kellner, Merck KGaA, Darmstadt

Biopharmaceuticals III—From Candidates to High Quality
Dr. Anne Arnold, Immundiagnostik AG, Bensheim
Dr. Roland Kellner, Merck KGaA, Darmstadt

Working Group Medical Informatics—Learning Health System and Laboratory Medicine
Dr. Andreas Bietenbeck, Klinikum rechts der Isar der Technischen Universität München

Clinical Mass Spectrometry in Metabolomics Applications
Dr. Christoph Seger, Labormediznisches Zentrum
Dr. Peter Findeisen, MVZ Labor Limbach & Kollegen, Heidelberg

Chromatography and Mass Spectrometry: Anything new? I / II / III
Dr. Oliver Schmitz, Universität Duisburg-Essen

ABC: Model-based Process Design and Control
Dr. Michael Maiwald, Bundesanstalt für Materialforschung und-prüfung (BAM)
Dr. Günter Gauglitz, Eberhard-Karls Universität Tübingen

Innovative Process Analytics
Dr. Tobias Eifert, Covestro Deutschland AG, Uerdingen

Trends in Electroanalysis
Dr. Frank-Michael Matysik, Universität Regensburg

Biobased and Biomimetic Sensing
Dr. Tilman Sauerwald, Saarland University

Targeted and Non-targeted Foodomics Correlated to Bioactivity and Authenticity
Dr. Michael Rychlik, TU München

Unraveling Emerging Contaminants in Foods by Modern Analytical Strategies
Dr. Michael Rychlik, TU München

Artificial Intelligence and Big Data in Medicine—Quo vadis?
Dr. Mustafa Porsch-Özcürümez, Ruhr-Universität Bochum

WEDNESDAY, APRIL 1

Metabolomics
Dr. Guowang Xu, DICP, Dalian

Advanced Microscopy
Dr. Annika Grüneboom, Universitätsklinikum Erlangen

Reference Intervals in Endocrinology—Is there a better way
Dr. Jürgen Kratzsch, Universitätsklinikum Leipzig
Dr. Martin Bidlingmaier, Klinikum der Universität München

Patient Safety and Test Utilization
Dr. Matthias Orth, Vinzenz von Paul Kliniken gGmbH/Marienhospital Stuttgart
Dr. Ralf Lichtinghagen, Medizinische Hochschule Hannover

Emerging Topics in Analytical Toxicology, Forensics, and Doping Control I—Isotope Ratio Mass Spectrometry (IRMS) in Analytical Toxicology
Dr. Hans Maurer, Saarland University

Emerging Topics in Analytical Toxicology, Forensics, and Doping Control II—Omics and MALDI Applications in Analytical Toxicology
Dr. Hans Maurer, Saarland University

Emerging Topics in Analytical Toxicology, Forensics, and Doping Control III—Protein Analysis and Alternative Sampling in Analytical Toxicology
Dr. Hans Maurer, Saarland University

New Approaches in the Analysis of Persistent and Mobile Organic Compounds
Dr. Thomas P. Knepper, University of Applied Science Fresenius, Idstein
Dr. Thorsten Reemtsma, Helmholtz-Centre for Environmental Research (UFZ), Leipzig

Non-target Screening in Future Water Monitoring
Dr. Torsten C. Schmidt, Universität Duisburg-Essen
Dr. Wolfgang Schulz, Zweckverband Landeswasserversorgung, Stuttgart

Analysis of Pathogens and Antibiotic-resistant Bacteria
Dr. Michael Seidel, Technische Universität München

ABC: Digital Analytical Sciences
Dr. Ulrich Panne, Bundesanstalt für Materialforschung und-prüfung (BAM)
Dr. Günter Gauglitz, Eberhard-Karls Universität Tübingen

ABC: Bioanalytics I—Nanomaterials in BioAnalysis
Dr. Antje Bäumner, Universität Regensburg

ABC: Bioanalytics II—Analytics Enabling the Concept of Anywhere Care
Dr. Günter Gauglitz, Eberhard-Karls Universität Tübingen

Quality in the Different Phases of Laboratory Medicine
Dr. Alexander von Meyer, Kliniken Nordoberpfalz AG, Weiden

Metrology meets Lifescience (working title)
Dr. Gavin O'Conner, Physikalisch-Technische Bundesanstalt (PTB), Braunschweig

THURSDAY, APRIL 2

New Technologies for OMICS Sample Preparation
Dr. Christian Scherling, Tecan, Kreilsheim

Lipidomics
Prof. Markus R. Wenk, Department of Biological Science; National University of Singapore

Liquid Profiling to Guide Cancer Therapies
Dr. Christof Winter, Klinikum rechts der Isar der Technischen Universität München
Dr. Georg Erich Hoffmann, Trillium GmbH, Grafrath

Current and Future Challenges in Analytical Spectrometry I—Bunsen-Kirchhoff-Award Session
Dr. Kerstin Leopold, Universität Ulm
Dr. Carsten Engelhard, Universität Siegen

Current and Future Challenges in Analytical Spectrometry II—Nano- and Single-Particle Techniques in Analytical Spectrometry
Dr. Kerstin Leopold, Universität Ulm
Dr. Carsten Engelhard, Universität Siegen

Current and Future Challenges in Analytical Spectrometry III—Laser and Imaging Techniques in Analytical Spectrometry
Dr. Kerstin Leopold, Universität Ulm
Dr. Carsten Engelhard, Universität Siegen

High Resolution Mass Spectrometry: Technologies and Applications I—Fourier Transform Cyclotron Resonance Mass Spectrometry (FTICR-MS)
Dr. Ralf Zimmermann, Helmholtz Zentrum München
Dr. Alan G. Marshall, Florida State University

High Resolution Mass Spectrometry: Technologies and Applications II—Orbitrap Mass Spectrometry
Dr. Ralf Zimmermann, Helmholtz Zentrum München
Dr. Alexander Makarov, Thermo Fisher Scientific, Bremen

High Resolution Mass Spectrometry: Technologies and Applications III—High Resolution Time-of-Flight Mass Spectrometry (HRTOF-MS)
Dr. Ralf Zimmermann, Helmholtz Zentrum München
Dr. Viatcheslav Artaev, LECO Corporation, Michigan

Forschungsdatenmanagement I - Innovation for Research Data Management and Mining
Sabine Brunger-Weiland, FIZ Karlsruhe–Leibniz-Institut für Informationsinfrastruktur GmbH

Forschungsdatenmanagement II - Data Management Aspects of Human Biobanking
Dr. Michael Kiehntopf, Universitätsklinikum Jena
Dr. Ronny Baber, Universitätsklinikum Leipzig

Forschungsdatenmanagement III
Dr. Wolf von Tümpling, Helmholtz-Zentrum für Umweltforschung (UFZ), Magdeburg

Pushing the Limits of Separation: Still Much To Discover
Dr. Martin Vogel, Universität Münster

Fishing for Protein Biomakers—Cutting-edge immunoassays
Dr. Oliver Poetz, Signatope GmbH, Reutlingen

CLINICAL TRIALS

BRIEFS

Easing enrollment woes

BOSTON—AG Mednet has unveiled a new addition to its clinical trial software-as-a-service (SaaS) platform: Judi // Eligibility, which helps to streamline central eligibility review workflows in clinical trials and aggregates data to help investigators find eligible participants more quickly.

"Judi // Eligibility automates and manages a challenging area of clinical trials—finding the right patients to make an accurate determination about the potential success of a new therapy," said Abraham Gutman, president and CEO of AG Mednet. "Enrolling the wrong patients disrupts data and slows a trial down. Until now, there has not been a way to centralize the decision-making process around patient recruitment and to implement checks and balances, so the trial and its sponsor have the right patient mix to move the trial forward. Judi // Eligibility solves that."

On to the clinic

GROSSE POINTE FARMS, Mich.—SciTech Development's Investigational New Drug (IND) application for ST-001 nanoFenretinide was accepted by the U.S. Food and Drug Administration, SciTech announced recently. This clears ST-001 nanoFenretinide, an experimental treatment for T-cell non-Hodgkin's lymphoma (NHL), to enter clinical trials. The first study will be conducted at the Rush University Medical Center, and will consist of patients with relapsed/refractory T-cell NHL, with a scheduled start date of mid-2020. ST-001 nanoFenretinide features a nanoparticle suspension to allow for intravenous administration.

Earle Holsapple, president of SciTech Development, commented in part that "FDA approval of our IND for ST-001 is a significant milestone in the development of our SciTech Drug Delivery Vehicle (SDV) program."

IN THIS SECTION

Good news from HARMONY

ACADIA's pimavanserin halts trial at interim analysis after meeting primary endpoint

BY KELSEY KAUSTINEN

SAN DIEGO—Of the roughly eight million individuals in the United States living with dementia, research suggests that some 30 percent of those patients suffer from psychosis. Dementia-related psychosis includes that seen in Alzheimer's disease, dementia with Lewy bodies, Parkinson's disease, vascular dementia and frontotemporal dementia.

ACADIA Pharmaceuticals is advancing pimavanserin, a candidate it hopes will provide a treatment for such patients. The company recently announced that the drug met its primary endpoint in the HARMONY study, which was stopped at the pre-planned interim analysis due to having significantly reduced risk of relapse of psychosis by 2.8-fold compared to placebo. Pimavanserin also met the key secondary endpoint by significantly reducing risk of discontinuation for any reason by 2.2-fold. Top-line results from the HARMONY study were presented at the 12th Clinical Trials on Alzheimer's Disease meeting held in December.

"These three indications, in addition to [Parkinson's disease psychosis], represent a potential 35-fold increase in the number of treated patients."
Stephen Davis, CEO of ACADIA Pharmaceuticals

The Phase 3 HARMONY study was a double-blind, placebo-controlled, relapse prevention study in 392 patients, meant to assess the safety and efficacy of pimavanserin as a treatment for delusions and hallucinations associated with dementia-related psychosis. Pimavanserin is a selective serotonin inverse agonist and antagonist that preferentially targets 5-HT2A, which is implicated in psychosis, schizophrenia, depression and other neuropsychiatric disorders. The drug

HARMONY CONTINUED ON PAGE 26

Pimavanserin, which is already approved in the United States for hallucinations and delusions associated with Parkinson's disease psychosis, is a selective serotonin inverse agonist and antagonist that preferentially targets 5-HT2A, which is implicated in psychosis, schizophrenia, depression and other neuropsychiatric disorders.

Full steam ahead in FSHD

Fulcrum advances losmapimod into Phase 2b trial

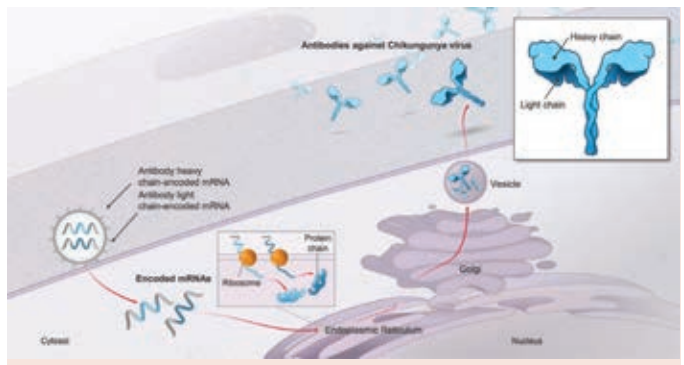
BY KELSEY KAUSTINEN

CAMBRIDGE, Mass.—Fulcrum Therapeutics Inc., a biopharmaceutical company focused on genetically defined rare diseases, is seeking to break new ground with losmapimod in facioscapulohumeral muscular dystrophy (FSHD), a rare form of muscular dystrophy. Losmapimod is a selective p38α/β mitogen activated protein kinase (MAPK) inhibitor.

Fulcrum has two trials underway for the compound at present, both of which were initiated late in 2019. ReDUX4 is a Phase 2b clinical trial meant to assess the safety and efficacy of losmapimod in addressing the underlying cause of FSHD. ReDUX4 is a randomized, double-blind, placebo-controlled, 24-week study to evaluate losmapimod's ability to reduce DUX4-driven gene expression as measured by a subset of DUX4-regulated gene transcripts in skeletal muscle biopsies. In conjunction with ReDUX4, Fulcrum also launched a 52-week open-label study.

In October, the company reported preliminary results from Phase 1 clinical trial of losmapimod in FSHD, which were also presented at the 24th International Annual Congress of the World Muscle Society. The trial sought to determine losmapimod's safety and efficacy in healthy volunteers as well as FSHD patients, in addition to determining repeated dose pharmacokinetics and target engagement in FSHD patients. The drug candidate demonstrated similar tolerability, safety and pharmacokinetics in both healthy participants and FSHD patients, with

FSHD CONTINUED ON PAGE 27



CREDIT: MODERNA INC.

Data from Moderna's antibody against the chikungunya virus has given the company enough confidence in its mRNA therapeutics delivery technology to add autoimmune and inflammatory disease modalities to its existing areas of infectious disease, immuno-oncology, rare disease and cardiovascular disease.

Riding success to autoimmune disease

Moderna follows clinical validation of systemic delivery with two more development candidates

BY JEFFREY BOULEY

CAMBRIDGE, Mass.—Moderna Inc. is looking for new fields to sow in the therapeutic world as it enters the realm of autoimmune and inflammatory diseases. But the clinical-stage biotech company—which says it is "pioneering messenger

MODERNA CONTINUED ON PAGE 28

HARMONY

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was approved in April 2016 by the U.S. Food and Drug Administration for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis under the name Nuplazid.

"The results presented today are an important advance for patients and caregivers who struggle with the burden of dementia-related psychosis where no FDA-approved treatment is currently available," said Dr. Jeffrey Cummings, director emeritus of Cleveland Clinic Lou Ruvo Center for Brain Health in Las Vegas. "Reducing the risk of relapse of psychotic symptoms by this magnitude is an important and meaningful outcome, as these are serious events which could lead to poor patient outcomes and a significant increase in caregiver burden and distress."

CREDIT: ACADIA PHARMACEUTICALS

ACADIA Pharmaceuticals is advancing pimavanserin, a drug candidate it hopes will provide help for patients with dementia-related psychosis.

The study included a 12-week open-label pimavanserin treatment period prior to randomization, during which 61.8 percent of eligible patients met pre-specified criteria for pimavanserin treatment response at weeks eight and 12, and were randomized into the double-blind portion of the study. In the open-label period, patient change from baseline to week eight and week 12 on the Scale for the Assessment of Positive Symptoms-Hallucinations and Delusions (SAPS-H+D) score improved by 63.0 percent and 75.2 percent, respectively.

Pimavanserin was well tolerated, with no further loss of cognition and no worsening of motor symptoms. Adverse events were seen at a rate of 41 percent in the double-blind period, with discontinuations due to adverse events of only 2.9 percent and serious adverse events of only 4.8 percent. One death was reported in the open-label period, and one death in the pimavanserin group during the double-blind period; investigators determined that neither was related to pimavanserin.

"We are extremely pleased to announce the top-line results from this landmark Phase 3 study in dementia-related psychosis," commented ACADIA's president, Dr. Serge Stankovic. "The HARMONY study was designed to answer three very important questions. First, in the 12-week open-label period, pimavanserin treatment showed a meaningful reduction of the symptoms and stabilization of psychosis across all of the five clinically diagnosed subtypes evaluated. Second, in the 26-week double-blind period, patients on pimavanserin had a nearly threefold reduction of risk of relapse compared to patients on placebo. And third, pimavanserin was well tolerated by elderly patients with dementia-related psychosis. We look forward to discussing these results with the FDA in the first half of 2020."

"Reducing the risk of relapse of psychotic symptoms by this magnitude is an important and meaningful outcome, as these are serious events which could lead to poor patient outcomes and a significant increase in caregiver burden and distress."

Dr. Jeffrey Cummings, director emeritus of Cleveland Clinic Lou Ruvo Center for Brain Health

ACADIA intends to meet with the FDA regarding a supplemental NDA submission. While pimavanserin has received Breakthrough Therapy Designation for the treatment of dementia-related psychosis, no drugs have yet been approved for that indication.

In a webcast of ACADIA Pharmaceuticals' presentation by CEO Stephen Davis at the 38th Annual J.P. Morgan Conference, Davis noted that in 2019, the company saw a 50-percent increase of pimavanserin sales growth year over year compared to 2018. He also pointed out that of the company's four late-stage programs, three feature pimavanserin: dementia-related psychosis, major depressive disorder (adjunctive therapy) and negative symptoms of schizophrenia.

"These three indications, in addition to [Parkinson's disease psychosis], represent a potential 35-fold increase in the number of treated patients," Davis remarked in the presentation, adding that dementia-related psychosis, major depressive disorder (with pimavanserin solely as an adjunctive therapy) and negative symptoms of schizophrenia represent market opportunities that are 10, 20 and five times the size of the Parkinson's disease psychosis market, respectively.

ACADIA is advancing pimavanserin through trials in all three of those indications, with results from its Phase 3 CLARITY-2 trial in major depressive disorder expected in the fourth quarter of 2020 and a second pivotal study in schizophrenia slated to begin this summer. ■

EDITCONNECT: E022016

Codexis and Nestlé Health Science team up

Companies look to advance GI therapeutic candidate CDX-7108

BY *DDNEWS* STAFF

REDWOOD CITY, Calif.—Codexis Inc., a protein engineering company and developer of novel biotherapeutics, and Nestlé Health Science, a globally recognized leader in the field of nutritional science, have signed an agreement to advance a lead candidate discovered through a strategic collaboration agreement (SCA) into preclinical development and early clinical studies. The SCA, signed in 2017, was an agreement to co-discover new enzyme therapy candidates for Nestlé Health Science's nutritional therapies portfolio.

The companies' new agreement will advance the development of CDX-7108, the lead candidate for a potential treatment of a gastrointestinal (GI) disorder. In parallel, the original SCA will be extended through the end of 2021 to support the discovery of therapeutic candidates for additional disorders.

"Our new and extended agreements with Codexis are a demonstration of the progress of the biotherapeutic pipeline as a result of our partnership, building on the previously established clinical success with CDX-6114 targeting phenylketonuria," said Greg Behar, CEO of Nestlé Health Science. "The CDX-7108 program is the first project performed under the SCA, and in less than two years from conceptualization, we have created an orally administrable enzyme candidate that meets our target criteria for advancement."

Added John Nicols, Codexis' president and CEO: "This partnership was initiated to leverage and extend the application of the CodeEvolver protein engineering platform and to create novel enzymes that will further fuel our biotherapeutics pipeline. Two years into the collaboration, we are excited to advance our first candidate into formal preclinical development. In parallel, it is equally satisfying to see Nestlé Health Science endorse the wider possibilities of creating value with our CodeEvolver technology by continuing our productive collaboration on other therapeutic concepts in this extended SCA chapter."

Under the development agreements, Codexis and Nestlé Health Science will retain joint ownership over the rights to CDX-7108 as they move this therapeutic enzyme candidate into preclinical and clinical development. ■

EDITCONNECT: E022019

FSHD

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dose-dependent pharmacokinetics and target engagement in blood.

In FSHD patients, losmapimod dosing led to dose-dependent concentrations in skeletal muscle, and an oral 15 mg dose taken twice a day resulted in sustained drug concentrations that led to a significant reduction of DUX4-driven gene expression in preclinical models of human FSHD myotubes (muscle fibers).

It's encouraging progress for a drug that failed its first indication. Fulcrum in-licensed losmapimod from GlaxosmithKline after the compound fell short in acute coronary syndrome.

"Losmapimod has previously been shown to have adequate safety and tolerability in over 3,500 patients and healthy volunteers across multiple indications, with no safety signals attributed to the drug in those trials. Until now, losmapimod had not been tested in patients with FSHD, nor was it known if it was muscle-penetrant in humans," Dr. Michelle Mellion, medical director at Fulcrum Therapeutics, commented in a press release. "The preliminary results from our Phase 1 clinical trial of losmapimod in patients with FSHD indicate that losmapimod was generally well tolerated and achieved dose-dependent concentrations in plasma and muscle believed to be adequate for efficacy based on preclinical pharmacology studies."

Mis-expression of DUX4 has been found to be the key to FSHD. While this gene is usually only expressed in embryonic development and then silenced, in FSHD it remains active and overexpressed, which results in muscle tissue degenerating and being replaced by fat. This progressive disease leads to a loss of skeletal muscle, which results in increasing physical disability.

Dr. Peter Jones—who is the Mick Hitchcock, Ph.D. Endowed Chair in Medical Biochemistry and an associate professor of pharmacology at University of Nevada, Reno School of Medicine—is a leading researcher into genetics and epigenetics related to muscle development and disease. In a report on FSHD and the role of DUX4 in the disease, Jones explained that FSHD is the result of genetic alterations at Chr 4q35. Specifically, deletions at Chr 4q result in FSHD1, while mutations at Chr 18p result in FSHD2. Regardless of the form, however, epigenetic dysregulation is common across all forms of the disease.

As noted in the presentation, "DUX4 encodes an early developmentally active transcription factor that is silent in healthy somatic cells," and as a result, "DUX4 expression is aberrantly increased in FSHD skeletal muscle." While most muscle diseases are the result of a loss-of-function mutation, FSHD is a gain-of-function disease. When DUX4 expression was modulated in experiments, they found that dose-dependent increases in DUX4 expression in skeletal muscle resulted in decreased muscle function and strength, and an increase in muscle histopathology.

"This is a devastating, progressive disease and unfortunately one where there are no drugs currently approved, and there are no industry-sponsored programs in the clinic, so it's an area where there's just tremendous unmet need for patients," says Bryan Stuart, chief operating officer at Fulcrum. He tells *DDNews* that the trials for losmapimod are advancing "right on schedule," and the company anticipates presenting top-line data in the third quarter of the year.

FSHD isn't the only muscle disease that Fulcrum is looking into, however. The company has discovery-stage programs underway to identify and validate targets in several other diseases, including Duchenne muscular dystrophy, Friedreich ataxia, myotonic dystrophy 1 and α-Synucleinopathies. ■

EDITCONNECT: E022017

CREDIT: FULCRUM THERAPEUTICS

Losmapimod is a selective p38α/β mitogen activated protein kinase inhibitor that Fulcrum Therapeutics is exploring for facioscapulohumeral muscular dystrophy, a rare form of muscular dystrophy.

SKYRIZI

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psoriasis." Dr. Anne Bowcock, a professor of genetics at Washington University School of Medicine in St. Louis, "has identified a gene mutation known as CARD14 that, when triggered, leads to plaque psoriasis," the National Psoriasis Foundation reports.

New to the ranks of therapeutics for this disease is Skyrizi, which recently posted strong data in a head-to-head Phase 3 study against Cosentyx in adults with moderate-to-severe plaque psoriasis. The drug was approved just this past April by the U.S. Food and Drug Administration (FDA) for the aforementioned indication, and is a joint effort between AbbVie and Boehringer Ingelheim.

Skyrizi from AbbVie (a researcher of which is pictured here) and Boehringer Ingelheim won approval from the U.S. Food and Drug Administration in April 2019 for moderate-to-severe plaque psoriasis.

CREDIT: ABBVIE

The trial in question was a randomized, open-label, efficacy assessor-blinded, active-comparator study to determine the safety and efficacy of Skyrizi vs. Cosentyx in adults with plaque psoriasis. Patients were randomized to receive either two 75 mg subcutaneous injections of Skyrizi at baseline, four weeks later and every 12 weeks after that, or two 150 mg subcutaneous injections of Cosentyx at baseline; at weeks one, two, three and four; and then every four weeks after that. Primary endpoints consisted of non-inferiority at week 16 and superiority at week 52, with secondary endpoints consisting of Psoriasis Area and Severity Index (PASI) 100 at week 52, a static Physician Global Assessment score of clear or almost clear (sPGA 0/1) at week 52, and PASI 75 at week 52. In this study, Skyrizi treatment led to significantly higher rates of skin clearance compared to Cosentyx, meeting the primary endpoint of non-inferiority at 16 weeks, at which point 74 percent of Skyrizi patients achieved PASI 90 (at least 90-percent improvement from baseline) vs. 66 percent of Cosentyx patients. Skyrizi met the second primary endpoint as well, showing superiority via PASI 90 data at week 52. Of the Skyrizi-treated patients, 87 percent achieved PASI 90 at 52 weeks, compared to 57 percent of Cosentyx-treated patients.

Skyrizi also outperformed Cosentyx in all ranked secondary endpoints, including PASI 100, PASI 75 and sPGA 0/1 at week 52.

"In this study, Skyrizi showed superior efficacy compared to Cosentyx in helping patients achieve and maintain high levels of skin clearance at week 52," Dr. Michael Severino, vice chairman and president of AbbVie, commented in a press release. "Head-to-head data like these are crucial to help patients and their doctors make informed treatment decisions. We are pleased to add these results to the growing body of evidence supporting Skyrizi as a differentiated treatment option for adults living with psoriasis."

Safety data for this study showed a safety profile for Skyrizi that is consistent with that seen in previous studies, with no new safety signals. In addition, the rate of adverse events between Skyrizi and Cosentyx were comparable, and the rate of serious adverse events was 5.5 percent in the former group and 3.7 percent in the latter. In terms of adverse events leading to discontinuation of the study, Skyrizi had a rate of 1.2 percent while Cosentyx had a rate of 4.9 percent.

Time will tell whether this strong performance will help Skyrizi usurp Cosentyx in the psoriasis market. Cosentyx has a bit of legacy for Skyrizi to overcome, having been approved by the FDA in January 2015 and holding a strong market share since then. Analysts are generally positive on the drug's potential, however.

Motley Fool's Brian Orelli noted that "Skyrizi has been off to a solid launch. The drug was approved by the Food and Drug Administration in April, and by the third quarter—the first full quarter on the market—AbbVie had already sold $76 million worth of the drug in the U.S. In the same quarter, Novartis booked $937 million in global sales of Cosentyx, suggesting AbbVie and Boehringer Ingelheim have plenty of room to run—although to reach that level, the healthcare companies would need to also beat Cosentyx in psoriatic arthritis and ankylosing spondylitis, both of which Cosentyx is also approved to treat."

Geoffrey C. Porges of SVB Leerink Research commented that "This is another study confirming the superiority of IL-23 inhibition to IL-17 inhibition as a treatment strategy in psoriasis."

"Skyrizi in particular offers the advantage of long-term three-monthly dosing, compared to monthly dosing with Cosentyx and Taltz. Today's positive head-to-head trial result increased our conviction that Skyrizi will continue to grow strongly and gain share from its competitors (Cosentyx annual sales ~ $3bn)," he added. "We currently forecast Skyrizi sales reaching $1bn this year, and growing to $2.7bn by 2022, before meaningful contributions from additional indications boost revenue, with total revenue ultimately reaching $6.5bn by 2028. Our Skyrizi forecast is 16-22 percent higher than the latest consensus for the 2020-2025 time frame and is a key element of our positive stance towards AbbVie's stock." ■

EDITCONNECT: E022002

MODERNA

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RNA (mRNA) therapeutics and vaccines to create a new generation of transformative medicines for patients"—is doing so with a solid base, building on work it has already done and riding the wave of clinical validation of systemic delivery of mRNA that was provided by data from its antibody against the chikungunya virus (mRNA-1944) program.

Along with that news, the company also announced that it will expand its pipeline of innovative vaccines in the near term, following six positive Phase 1 clinical trial readouts from its infectious disease portfolio and the initiation of a Phase 2 study for its cytomegalovirus (CMV) vaccine, designated mRNA-1647.

While Moderna's pipeline is organized into six modalities, they are all based on similar mRNA technologies, delivery technologies and manufacturing processes, and the announcements derive from the fact that the company is confident that recent positive Phase 1 data from its infectious disease vaccine portfolio, including its complex CMV vaccine, and its chikungunya antibody program have de-risked its prophylactic vaccines and systemic therapeutics modalities.

Essentially, the company's strategy is to leverage early programs within a modality to generate clinical data and insights that reduce the technology risk of subsequent programs and can accelerate the pace of expansion into new modalities.

As an initial step to adding autoimmune indications as part of its pipeline work, Moderna plans to conduct a Phase 1 study of mRNA-6231 in healthy adult volunteers and intends to pursue proof of concept with mRNA-6981 in a Phase 1 study in type 1 autoimmune hepatitis.

"2019 was an inflection point for Moderna, with significant clinical advances resulting from our investments in science and manufacturing capabilities. The positive Phase 1 results from our CMV vaccine and chikungunya antibody programs validate our approach and help clinically de-risk the delivery technologies for our prophylactic vaccines and systemic therapeutics modalities. Based on these learnings, we are excited to enter a new therapeutic area in autoimmune disease and announce two new development candidates," said Stéphane Bancel, Moderna's CEO. "We are entering 2020 with clear priorities, a strong cash balance and a talented team of employees focused on achieving our mission. With our CMV vaccine, we are preparing for our first pivotal Phase 3 study, and we look forward to announcing additional new development candidates in our two clinically de-risked modalities, prophylactic vaccines and systemic therapeutics."

Moderna currently has 21 mRNA development candidates in its portfolio and 13 of those are now in clinical studies.

As Moderna puts it, autoimmune diseases are characterized by immune activation in response to antigens normally present in the body, reflecting a loss of tolerance. Within this therapeutic area, the company is developing two potential medicines, mRNA-6231 and mRNA-6981, designed to engage peripheral tolerance pathways to dampen autoimmune activation and help restore immune homeostasis, thereby reducing autoimmune pathology.

mRNA-6231 is an mRNA encoding for a long-acting IL-2 mutein designed to preferentially activate and expand the regulatory T cell population, dampening the immune response, while mRNA-6981 is an mRNA encoding for PD-L1 and is designed to augment cell surface levels of PD-L1 on myeloid cells, providing co-inhibitory signals to self-reactive lymphocytes.

As an initial step to addressing a range of autoimmune indications, the company plans to conduct a Phase 1 study of mRNA-6231 in healthy adult volunteers and intends to pursue proof of concept with mRNA-6981 in a Phase 1 study in type 1 autoimmune hepatitis, a condition that involves liver inflammation and can lead to cirrhosis and liver failure. The Phase 1 study of mRNA-6231 will be the first clinical demonstration of subcutaneous administration of this delivery technology.

Both of these new autoimmune development candidates share the same delivery technology as mRNA-1944, the antibody against chikungunya. The autoimmune therapeutic area is Moderna's fifth therapeutic area, joining the areas of infectious disease, immuno-oncology, rare disease and cardiovascular disease.

Moderna also provided a financial update around the same time, noting that it is experiencing continued growth across the organization, having ended 2019 with approximately 820 full-time employees, compared to 735 employees the year before. In addition, reiterating prior guidance, the company expects 2020 net cash used in operating activities and purchases of property and equipment to be between $490 million and $510 million. Moderna currently has strategic alliances for development programs with AstraZeneca and Merck Inc.; the Defense Advanced Research Projects Agency, an agency of the U.S. Department of Defense; and the Biomedical Advanced Research and Development Authority, a division of the Office of the Assistant Secretary for Preparedness and Response within the U.S. Department of Health and Human Services. ■

EDITCONNECT: E022018

DIAGNOSTICS

BRIEFS

Assay assembly

ANN ARBOR, Mich. & MILAN—A new partnership is underway between NeuMoDx Molecular and Sentinel Diagnostics for the development of multiple diagnostic assays for the NeuMoDx 96 and 288 Molecular Systems. NeuMoDx's analyzers allow users to load up to 288 patient samples in a continuous, random-access workflow for high-throughput sample processing. Sentinel has developed STAT-NAT, a proprietary technology that stabilizes the activity of PCR mix to allow for room-temperature transport/storage, improved performance and a long shelf life. In this collaboration, Sentinel's real-time PCR assays will be adapted to the NeuMoDx 96 and 288 Molecular Systems and incorporate the STAT-NAT technology. The resulting test menu will include assays for detecting post-transplant infections, parasitic/hospital-acquired infections, respiratory infections and for pharmacogenetic applications.

Home monitoring for hemophilia

NIJMEGEN, The Netherlands—Enzyre and Takeda Pharmaceutical Co. Ltd. are working together under a research collaboration agreement to develop a diagnostic device for hemophilia patients to monitor their coagulation status at home. Per the agreement, Takeda will provide Enzyre with funding to allow the latter to further develop its technology. The goal is an option that will enable automatic determination of coagulation status and immediately transmit test results to a patient's physician via a mobile app.

"Diabetics have long been able to individually manage their disease through home glucose measurement, and we are determined to make this the case for those living with hemophilia," stated Dirk Pollet, CEO of Enzyre. "With our proprietary technology, we aim to provide hemophilia patients and their caregivers with peace of mind by allowing them to monitor coagulation status at home. Ultimately, we'd like to empower these patients to live a normal life."

IN THIS SECTION

Analysis pairs up with immunotherapy

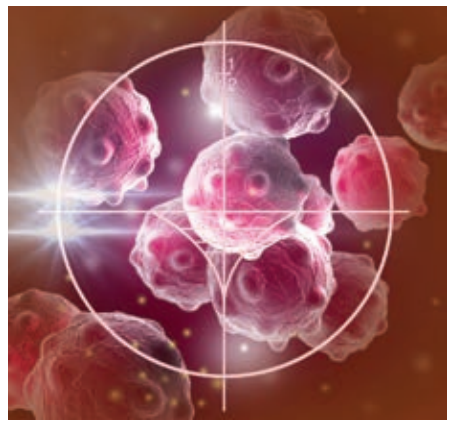
Shimadzu and Providence Cancer Institute team up to advance cancer immunotherapy research

BY MEL J. YEATES

COLUMBIA, Md. & PORTLAND, Ore.—Shimadzu Corp. and the Earle A. Chiles Research Institute, a division of Providence Cancer Institute, have entered into a joint research agreement to apply mass spectrometry technology to develop tools for personalized cancer immunotherapeutics.

"In collaboration with Shimadzu, we want to build better diagnostics based on each patient's unique tumor microenvironment," stated Dr. Brian Piening, technical director of Clinical Genomics and assistant member of the Immune Omics Laboratory at Providence. "This will help inform clinical care with current immunotherapies and pave the way for the next generation of personalized immunotherapeutics."

"After several discussions, [Shimadzu and Providence] decided to collaborate for the development of a novel strategy for cancer immunotherapy focusing on microenvironment," says Dr. Takashi Shimada, R&D manager, Shimadzu Bioscience Research Partnership, Shimadzu Scientific Instruments (SSI). "With the cooperation and support of Dr. Bernard Fox and Dr. Yoshinobu Koguchi, I drafted the entire study concept of the research strategies and the plan of a new Shimadzu bioscience lab/equipment in Bothell, Wash."

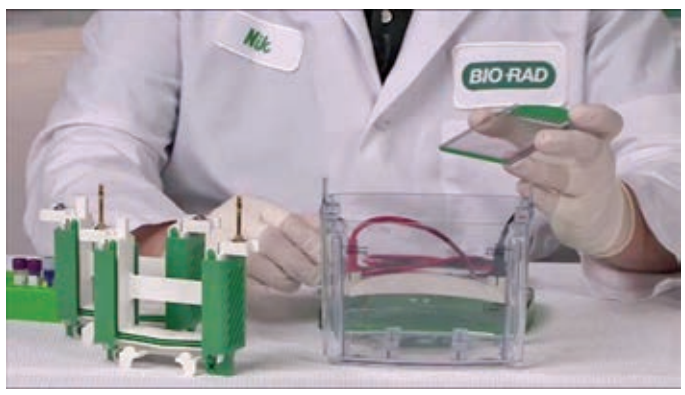


Shimadzu and Providence Cancer Institute plan to develop technologies to reliably identify cancer antigens recognized by an individual's immune system, and to analyze the pharmacokinetics of immunotherapy drugs.

Shimadzu and Providence plan to develop technologies to reliably identify cancer antigens recognized by an individual's immune system, and to analyze the pharmacokinetics of immunotherapy drugs. The companies share a goal of bringing these novel diagnostics to early clinical application.

"For the new strategy of cancer immunotherapy, we focus on two approaches. One approach is to elucidate pharmacokinetic behavior of therapeutic antibodies (mainly immune checkpoint inhibitors) in circulation and tumor tissues. Precise antibody monitoring of the distribution at the tumor site will be able to apply for the novel development of individualized dosing method. The other approach is to determine the cancer antigen peptides on human leukocyte antigen (HLA)," Shimada adds. "The technology to identify new antigen peptides that respond to immune cells with high efficiency will be applicable to prediction

SHIMADZU CONTINUED ON PAGE 30



CREDIT: BIO-RAD LABORATORIES

Bio-Rad Laboratories Inc. has announced that its droplet digital PCR offering provides the most sensitive, precise and rapid method of diagnosing and monitoring leukemia.

WHY WAIT?

Bio-Rad's ddPCR technology provides faster, more accurate diagnoses

BY LORI LESKO

HERCULES, Calif.—As the industry searches for a faster way to diagnose and treat blood disorders, life-sciences company Bio-Rad Laboratories Inc. has announced that its droplet digital PCR (ddPCR) technology fits the bill by providing a more sensitive, precise and rapid method of diagnosing and monitoring leukemia than any counterpart.

Scientists attended the American Society of Hematology (ASH) conference in Orlando in December, presenting more than 40 abstracts highlighting research, driven in part Bio-Rad's ddPCR technology. Some of the work illustrated how a simple blood test, using ddPCR,

DDPCR CONTINUED ON PAGE 31

Advancing genomics

Illumina announces new sequencing system, partnership with Roche and a software suite to accelerate genomics adoption

BY JEFFREY BOULEY

SAN DIEGO—Illumina Inc. wants to give more people on the bench access to next-generation sequencing (NGS), and part of that effort involved building the NextSeq 2000 Sequencing System and NextSeq 1000 Sequencing System "from the ground up" and pushing the TruSight Software suite to help accelerate adoption of genomics—all to demonstrate "its commitment to making genomics more accessible for the potential benefit of patients" and "to unlocking the power of the genome."

The NextSeq 2000 Sequencing System, the latest NGS system from Illumina, reportedly offers innovative design features, advanced chemistry, simplified bioinformatics and an intuitive workflow that enable the widest range of applications on a benchtop sequencing system. The system is available this quarter, while the NextSeq 1000 Sequencing System is expected to begin shipping in the fourth quarter of 2020.

"Almost everything is new," said Francis deSouza, CEO of Illumina. The company noted in a statement that they incorporate more than 75 innovations, including two brand-new technologies: so-called super resolution optics and blue/green SBS chemistry, which will together enable a substantial increase in density and throughput as well as a reduction in operating costs. Further elaborating on this at a recent JP Morgan meeting, deSouza stated that the super-resolution optics are

GENOMICS CONTINUED ON PAGE 30

Further into oncology and NGS

NeoGenomics acquires oncology operation from Human Longevity for $37 million

BY JEFFREY BOULEY

FT. MYERS, Fla.—NeoGenomics Inc. announced recently that it had acquired the Oncology Division assets of Human Longevity, Inc. for $37 million.

The Oncology Division of Human Longevity performs next-generation sequencing (NGS) services for pharmaceutical customers. The division generated approximately $10 million in revenues in 2019 and ended the year with a backlog of approximately $15 million of signed contracts.

"The acquisition of the Oncology Division assets from Human Longevity significantly enhances our position as a leading provider of pharma services and next-generation sequencing," said Douglas M. VanOort, chairman and CEO of NeoGenomics. "This acquisition will expand our Pharma Services menu to include germline, whole-exome and whole-genome sequencing. We are delighted to add an experienced, specialized molecular workforce with strong next-generation sequencing expertise, particularly in servicing pharmaceutical customers, and I am pleased to welcome the Human Longevity Oncology Division employees to NeoGenomics."

Leerink Partners analysts wrote that NeoGenomics is "a uniquely positioned one-stop oncology testing service provider with an expanding market position following their acquisition of Genoptix—positioning the company at the diagnostics center of the 'oncology revolution' in healthcare."

Continued Leerink in an investors note: "Though acquisition is relatively small compared to their two most recent acquisitions, (~$139M for Genoptix in 2018 and ~$275M for Clarient in 2015), we are pleased to see NEO is investing in building out its comprehensive pharma services offering. NGS remains a key growth for NEO and based on our conversations with management, we believe the acquired division can grow 50 percent+ in 2020, implying $15M in revenues, and a ~2.5x sales acquisition multiple." ■

EDITCONNECT: 022023

SHIMADZU

CONTINUED FROM PAGE 29

of therapeutic efficacy, cell therapy and vaccine development."

"The most attractive feature of mass spec is the simultaneous and multiplex analysis of biological molecules with high selectivity/sensitivity from clinical samples," he explains. "With appropriate approaches and sample processing methods, this is far superior to other analytical technologies. The appropriate level of antibody dosage in each cancer treatment is still unclear. Our aim is to provide these criteria for precise therapy and cost. Combining with current information of cancer biomarkers and oncogenes, this criterion is determined from antibody pharmacokinetics, HLA peptides and immune cell distribution, and is an important signature in individualized medicine. And we want to promote our business of mass spec and related reagents/consumables in cancer immunotherapy area of U.S. and global market from 2020."

"We have an original method for monoclonal antibody analysis, nSMOL (nanosurface and molecular orientation limited proteolysis) technology, published by Dr. Iwamoto of Shimadzu. This is a novel Fab–selective proteolysis that is independent of a variety of monoclonal antibodies, and makes it easy to determine the antibody level in many biological samples. Based on the nSMOL technology, we will develop a new method for antibody monitoring in cancer tissue from biopsy, resection and formalin-fixed paraffin-embedded (FFPE) tissues," Shimada continues. "And for cancer antigens, we will develop an identification method of HLA peptides using a peptidomics and bioinformatics platform. Since the determination of HLA peptides essentially requires a data science approach, we will integrate the information provided by Providence genetic analysis from clinical patients with mass spec data."

SSI plans to direct the collaboration through the company's Innovation Center in Columbia, Md., and a new bioscience laboratory in Canyon Park in Bothell.

"It is a great honor that Shimadzu mass spectrometry can contribute to cancer immunotherapy pioneered by Dr. James Allison and Dr. Tasuku Honjo. At the minimum, the possibility that our mass spec technology could be applied to diagnostic techniques in cancer immunotherapy is a major motivation for us," Shimada remarks. "We will continue to apply new developments and make many medical contributions with our best effort."

SSI has also recently introduced to the market a new UV-i group of UV-Vis spectrophotometers, which are designed to provide improved quality control productivity, data analysis and management, and operating efficiency. The new series consists of six models: UV-1900i, UV-2600i, UV-2700i, UV-3600i Plus, SolidSpec-3700i and SolidSpec-3700i DUV.

The six spectrophotometers in the series include an automatic pass/fail determination for improved efficiency. The systems are equipped with a spectral evaluation function in the software that automatically determines whether data satisfies specified criteria. This function reportedly helps to improve the efficiency of quality control operations by eliminating the manual data analysis steps needed after spectra are acquired.

The UV-i spectrophotometers also include automatic measurement for improved operating efficiency. By connecting an autosampler unit, the systems can analyze up to 360 samples automatically. When used in combination with the spectral evaluation function, the entire process—including pass/fail determination—can be fully automated. Shimadzu also says that the new spectrophotometers will improve data analysis and data management. ■

EDITCONNECT: 022020

GENOMICS

CONTINUED FROM PAGE 29

capable of "breaking the diffraction limit" and are reportedly achieving what has been achieved on no other commercial sequencer. Meanwhile, the blue/green SBS chemistry allows a greater separation of signals, so they can be closer together, the company adds.

This total package could promise a more than 30-fold increase in data density, according to deSouza.

The platforms are also the first to incorporate Dragen processing on board, featuring both local and cloud-based options for run setup, management and analysis. The two new sequencers are expected to find ready homes in areas like single-cell RNA-seq, circulating tumor DNA analysis, and a variety of oncology panels.

The company's TruSight Software Suite v1.0, meanwhile, is said to deliver "ready-made infrastructure to adopt, ramp and realize the full potential of genome sequencing in rare and undiagnosed genetic disease. TruSight Software enables sample-to-report for genetic disease making it easier to access the valuable insights enabled by sequencing with comprehensive variant class analysis for greatest diagnostic yield."

The NextSeq 2000 will have a maximum sequencing data output of 300 Gb and a U.S. list price of $335,000, while the NextSeq 1000 will have a maximum output of 120 Gb and a U.S. list price of $210,000.

"We are proud to continue our tradition of driving down the cost of sequencing without compromising accuracy," commented Omead Ostadan, senior vice president of marketing and products at Illumina. "NextSeq 1000 and 2000 are designed to enable core labs, small to medium research labs and clinical facilities to access high-intensity sequencing applications using our industry-leading SBS technology."

Looking forward, deSouza expects both new-to-sequencing customers and existing NextSeq customers to transition to the new platforms.

In other news shared at the same time as the new NGS systems, Illumina and Roche announced a 15-year, non-exclusive collaboration agreement to broaden the adoption of distributable NGS testing in oncology. As the understanding of genomic drivers of cancer evolves, NGS has the potential to transform cancer risk prediction, detection, diagnosis, treatment and monitoring.

This agreement brings together complementary capabilities of each company to broaden global adoption of NGS in cancer care. As part of this agreement, Illumina will grant Roche rights to develop and distribute *in-vitro* diagnostic (IVD) tests on Illumina's NextSeq 550Dx System, as well as on its future portfolio of diagnostic (Dx) sequencing systems, including the forthcoming NovaSeqDx. Roche will in turn collaborate with Illumina to complement Illumina's comprehensive pan-cancer assay, TruSight Oncology 500 (TSO 500), with new companion diagnostic (CDx) claims. The financial terms of the deal were not disclosed.

"We are proud to continue our tradition of driving down the cost of sequencing without compromising accuracy. NextSeq 1000 and 2000 are designed to enable core labs, small to medium research labs and clinical facilities to access high-intensity sequencing applications using our industry-leading SBS technology."

Omead Ostadan, senior vice president of marketing and products at Illumina

Under the IVD terms of the agreement, Roche will develop, manufacture and commercialize AVENIO IVD tests for both tissue and blood for use on Illumina's NextSeq 550Dx System. Illumina will continue to sell the NextSeq 550Dx Systems and core sequencing consumables. Under the CDx terms of the agreement, Illumina and Roche will develop tests and pursue CDx claims on TSO 500 for both existing and pipeline oncology targeted therapies on the NextSeq 550Dx System. Illumina will lead the development and regulatory approval process, and will continue to manufacture, supply and commercialize TSO 500. Roche will support the development of the claims and regulatory filings.

"We are excited Roche has selected Illumina's sequencers as their platform of choice to accelerate the adoption and broaden the reach of oncology-based, distributable IVD tests into clinical care," said deSouza. "This partnership complements and strengthens our strategy to establish TSO 500 as a comprehensive NGS panel for cancer therapies by expanding the supported set of CDx claims on this universal panel. Building on the momentum of other recently established diagnostic and pharmaceutical partnerships, together we aim to advance critical access to NGS testing to improve patient outcomes."

Illumina also announced the development of a regulatory-cleared version of the high-throughput NovaSeq system to address growing demand for a Dx platform to support deeper sequencing at higher throughput. NovaSeqDx extends the company's portfolio of Dx cleared systems and, ahead of commercial availability targeted for 2022, will be available to IVD partners, including Roche, for content development.

"At Illumina, we are focused on three key areas to scale the reach and impact of genomics—enabling breakthrough genomics research, accelerating the clinical adoption of genomics and delivering fundamentally enabling technology innovations," deSouza remarked. "The NextSeq 1000 and 2000 Sequencing Systems, TruSight Software and our partnership with Roche, will accelerate the adoption of research and clinical sequencing for the benefit of humanity." ■

EDITCONNECT: 022022

DDPCR

CONTINUED FROM PAGE 29

can predict treatment outcomes for leukemia patients, leading to improving patients' lives by helping their physicians determine the right treatment at the right time and enabling clinicians to monitor biomarkers of malignant and nonmalignant blood disorders cost-effectively and at scale.

Other conference posters demonstrated how ddPCR has been used to monitor patients with hairy cell leukemia (HCL) and chronic myeloid leukemia (CML), particularly in cases when testing must identify low levels of the biomarkers to provide an early indication of whether or not a patient is responding to treatment.

Two researchers from the University of Bologna, Italy—Dr. Pier Luigi Zinzani, head of the Lymphoma Unit and a professor of hematology, and Alessandro Broccoli, research fellow in the Department of Experimental, Diagnostic and Specialty Medicine—had searched for a more sensitive test to determine if patients with HCL were in complete response after cladribine (2CdA) treatment. But after using ddPCR, the Italian researchers demonstrated how patients with active disease display a higher fractional abundance of BRAF V600E ctDNA than patients in complete response.

With ddPCR, Broccoli was able to measure the ctDNA and find residual HCL DNA in the blood following treatment with cladribine (CdbA), indicating the cancer would likely return earlier than expected.

"The study we presented last December at ASH, in fact, indicates that some patients with a long-lasting (> 5 years) complete response after one course of cladribine display no evidence of the BRAF V600E mutation, regarded as the key molecular event in the pathogenesis of the disease in peripheral blood," Broccoli explains. "On the contrary, patients with active disease (i.e. disease at onset or relapse, meeting the criteria for the initiation of an effective treatment) display a positive assay, and in any case with a fractional abundance of the mutated allele (always higher than 1 percent)."

"Given that HCL displays only a few leukemic circulating cells, even when the disease is active, a very sensitive assay is required to detect even a small fraction of affected (mutated) cells—and ddPCR shows more sensitivity than other quantitative PCR methods," he adds.

CREDIT: BUSINESS WIRE

The NextSeq 2000 Sequencing System, the latest next-generation sequencing system from Illumina, reportedly offers innovative design features, advanced chemistry, simplified bioinformatics and an intuitive workflow that enable the widest range of applications on a benchtop sequencing system.

Broccoli argues that with ddPCR, researchers must take steps "to assess comparability between peripheral blood and bone marrow samples in defining a molecular negativity/positivity of the assay (depending on different disease time-points: onset, relapse, first response, long-lasting first response, further complete response), to define a new category of 'molecular responders' that may better categorize patients in terms of long-term prognosis and tendency to relapse over time." They must also "define a threshold for fractional abundance to discriminate between negative results, minimal residual disease with no evidence of active disease and active disease."

With the goal of evaluating the potential diagnostic value of ddPCR in monitoring tyrosine kinase (TKI)-treated patients with CML, Carmen Fava, assistant professor at the University of Turin, Italy, and her colleagues recently conducted a multi-centric study comparing ddPCR with the standard method of reverse transcription quantitative PCR (RT-qPCR).

Fava found that ddPCR is just as effective as RT-PCR at detecting minimal residual disease in CML under TKI treatment, and that ddPCR is more precise than RT-PCR at low levels of residual disease.

"[The] ddPCR kit's reproducibility, ability to express results in IS and promising findings in several trials and reports, suggest ddPCR's potential extends to routine use in clinical settings to determine when treatment can be discontinued," Fava says.

For TKI-resistant patients with CML, ddPCR enables more timely changes in treatment than NGS Sanger sequencing, a common method used to detect BCR-ABL1 mutations which causes TKI treatment resistance among patients with CML who don't respond well to therapy, Fava explains.

Simona Soverini, assistant professor of the Department of Experimental, Diagnostic and Specialty Medicine of the University of Bologna, and other researchers recently tested next-generation sequencing (NGS) and a novel ddPCR based multiplex assay as potential alternatives to Sanger sequencing for screening a panel of 13 BCR-ABL1 mutations relevant for TKI selection. She found that she could use ddPCR to detect resistance mutations in TKI-resistant CML patients faster than NGS. Within the first 24 hours, ddPCR showed its superiority by yielding its findings in just one day, compared to 15 working days for NGS. ■

EDITCONNECT: 022021

BLOOD

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from around 1,000 women with breast cancer whose cancer had returned after treatment or had spread to another part of the body. The researchers wanted to determine whether taking a liquid biopsy, where traces of tumor DNA circulating in the blood could be detected, was a faster and easier alternative to traditional tumor testing.

The new study was designed to determine whether a blood test could detect three targetable defects in HER2, ESR1 and AKT1 genes, which are known to drive breast cancer. In the study, 142 women with these detectable mutations received experimental targeted therapies against the specific characteristics of their cancer. Treatments that have shown initial promise will be tested further in larger clinical trials. To validate their findings, the researchers also checked tissue samples from the patients and confirmed that the liquid biopsy had correctly identified the presence or absence of the mutations in over 95 percent of the cases. These findings suggest that the blood test could be a robust way to identify rare subtypes of breast cancer and could potentially replace the more invasive methods of analyzing breast tumors.

According to Nicholas Turner, professor of molecular oncology at The Institute of Cancer Research, London, and consultant medical oncologist at The Royal Marsden, "The choice of targeted treatment we give to patients is usually based on the mutations found in the original breast tumor, but their cancer can have different mutations after it has moved to other parts of the body. We have now confirmed that blood tests can quickly give us a bigger picture of the mutations present within multiple tumors throughout the body, getting the results back to patients accurately and faster than we could before. This is a huge step in terms of making decisions in the clinic, particularly for those women with advanced breast cancer who could quickly be put on new targeted treatments matched to their cancer if it evolves to become drug-resistant."

As part of research by Cancer Research UK, scientists at The Institute of Cancer Research, London, and The Royal Marsden NHS Foundation Trust analyzed the blood from around 1,000 women with breast cancer whose cancer had returned after treatment or had spread to another part of the body.

The researchers maintain that the blood tests are reliable enough to be used routinely by doctors once they have passed regulatory approval. For the targeted drugs still in development, the next step is to carry out larger clinical trials to determine whether they are better than existing treatments.

As Prof. Carlos Caldas, senior group leader at the Cancer Research UK Cambridge Institute, said, "This work builds on increasing evidence in favor of liquid biopsies. It's another step in the right direction and could mean a lot to people with advanced breast cancer, because it can identify those who may benefit from new targeted treatment after other options have stopped working. Liquid biopsies are also showing promise beyond guiding treatment choices. It's relatively easy to take a blood sample, which means the test could be used to monitor how cancer responds throughout a course of treatment, or it may be able to detect the early signs of treatment resistance." ■

CREDIT: CANCER RESEARCH UK

"We have now confirmed that blood tests can quickly give us a bigger picture of the mutations present within multiple tumors throughout the body, getting the results back to patients accurately and faster than we could before," says Nicholas Turner at The Institute of Cancer Research in London of recent findings released by Cancer Research UK (pictured here).

EDITCONNECT: E022003

CONTRACT SERVICES

BRIEFS

Simbec-Orion nets key honor by Lifestars

LONDON—As 2019 ended, Simbec-Orion shared news that it had been named the winner of the CRO of the Year award at the 2019 Lifestars Awards, which are organized by LSX and took place during the Investival Showcase and Jefferies Annual Healthcare Conference week in London. Simbec-Orion is a full-service boutique CRO with a focus in fields such as oncology, rare/orphan diseases and translational medicine.

"I am absolutely honored to accept this award on behalf of Simbec-Orion and to share it with our amazing team of clinical research professionals," said CEO Dr. Fabrice Chartier. "This award acknowledges the commitment we have made to structure our business to meet the needs of small and midsize drug developers, developing new therapies in rare disease and oncology."

Nanion Technologies and Assay.Works partner up

MUNICH, Germany—Nanion Technologies, a leading provider of automated electrophysiology systems, recently announced a partnership with Assay.Works, experts in assay development and high-throughput screening, who will be providing SURFE²R 96SE assays for membrane transporter research.

Membrane transport proteins, which enable active and secondary active transport of ions and solutes across the membrane, are important drug targets but may also be involved in unwanted side effects. Nanion's SURFE²R platform employs label-free, SSM-based electrophysiology to resolve small currents of transporters and pumps.

Said Dr. Ralf Schwandner, CEO of Assay.Works: "We are excited to deepen our long-standing relationship with the electrophysiology experts at Nanion. Their SURFE²R platform perfectly fits our mission to develop and apply predictive and scalable assays for therapeutics discovery."

IN THIS SECTION

Change continues for CDMOs

Capstone Headwaters report highlights increased growth, transactions in pharmaceutical outsourcing

BY KELSEY KAUSTINEN

BOSTON—Contract development and manufacturing organizations (CDMOs) and contract research organizations (CROs) comprise a significant—and growing—part of the drug development market as companies seek to outsource part or all of their development work in an effort to streamline the process and costs. Capstone Headwaters released its "Q3 Pharmaceutical Outsourcing Mergers & Acquisitions (M&A) Update" near the end of 2019, providing a snapshot of the market and its rapid growth. Eric Williams and Mark Surowiak, managing director and director of Capstone Headwaters, respectively, contributed to the report.

"The industry continues to benefit from a record number of drugs under development, ample venture capital allocated to biotech ventures, rising number of drugs securing FDA approval, and a rise in research and development initiatives targeting rare diseases," the report stated. "Not surprisingly, the second most common reason to outsource, as reported in Contract Pharma's 2018 outsourcing survey, was the fact that the drug sponsor was a virtual company. Additionally, as development, testing, manufacturing, quality control and regulatory issues become more complex, even the largest pharmaceutical companies are seeking outsourced partners who can augment internal capabilities and offer solutions that can shorten time to market, streamline and optimize the regulatory process, lower manufacturing costs and boost R&D productivity."

As noted in a recent report from Capstone Headwaters, "as development, testing, manufacturing, quality control and regulatory issues become more complex, even the largest pharmaceutical companies are seeking more outsourced partners."

A key driver is the increased interest in rare/orphan diseases. Categorized by the FDA as diseases affecting fewer than 200,000 individuals, the opportunity for market dominance is significant for whichever company can get a drug or therapeutic to market first in a given indication. However, the rarity of the disease, and relative paucity of patients compared to broader indications such as diabetes or neurodegenerative disease, also means there is a need to streamline and

CAPSTONE CONTINUED ON PAGE 33

PROVIDING BETTER SERVICE FOR VESICLES ANALYSIS

Exosomics implements NanoFCM's NanoAnalyzer at its Siena site

BY *DDNEWS* STAFF

SIENA, Italy & NOTTINGHAM, U.K.—Exosomics SpA, which bills itself as the leading extracellular vesicles biotech company, recently announced that it has implemented NanoFCM's NanoAnalyzer instrument to offer "sophisticated" contract research and measurement services worldwide. In this strategic partnership, Exosomics becomes NanoFCM's approved service supplier of nano-flow cytometry measurements. These can be performed as a standalone service or coupled to solutions provided by Exosomics.

TOOLS & TECHNOLOGY

"Thanks to their NanoAnalyzer, Exosomics will be able to supply the widest range of nano-flow cytometry measurements, which are in high demand across Europe and the rest of the world," said Dr. Dimitri Aubert, managing director of NanoFCM. "We are delighted to recommend Exosomics to our close collaborators wishing to access the NanoAnalyzer platform on a punctual

VESICLES CONTINUED ON PAGE 33

Deepening DMPK at Sygnature

Company development also bolsters subsidiary's kidney disease and fibrosis capabilities

BY MEL J. YEATES

NOTTINGHAM, U.K.—Sygnature Discovery announced in January that it has further strengthened its drug metabolism and pharmacokinetics (DMPK) capabilities with the addition of several new senior scientists to the management team.

Clive Dilworth has been recruited as director of DMPK. He replaces Tim Schulz-Utermoehl, who had been heading up the DMPK team on a part-time basis. Schulz-Utermoehl now plans to focus on his work with several biotech start-ups,.

Dilworth joins from a management role at the Alderley Park life-science campus, where he provided strategic and scientific guidance for startups and contract research organizations (CROs) at the site. Prior to this, Dilworth spent 20 years working in DMPK roles at various CROs, most recently Cyprotex

DMPK CONTINUED ON PAGE 33

CAPSTONE

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minimize costs as much as possible to manage risk and ensure a return on investment. Another consideration is the infrastructure needed to develop a product for a single indication, which can be prohibitively costly. As such, many companies seek to outsource rare disease drug development, which allows them to make use of CROs or CDMOs with existing capabilities, rather than investing heavily in production equipment and infrastructure for a drug that may not make it to market for a smaller than usual market size.

Given the forecasted potential for the orphan disease market, however, it's no wonder that many companies consider it worth the risk. In 2018, 59 new drugs were approved, and of those, more than half were for rare diseases. The report states that according to EvaluatePharma, global orphan drug sales are expected to reach $242 billion by 2024, comprising 20.3 percent of all prescription sales. In 2020, that number is expected to rise from last year's $136 billion to $150 billion.

Additionally, the types of drugs being approved are also impacting the CDMO industry. Biologics are on the rise, and where once they accounted for only two, three or four of all drugs approved in a given year, that dynamic has changed. In 2014, 2015, 2017 and 2018, 10 or more of the drugs approved annually were biologics.

The rising number of biologics-based drugs and therapeutics has also contributed, as the nature of these molecules requires developers to meet additional or more stringent regulatory standards. And given that moving a drug from discovery to commercialization takes an average of 10 years and $1 billion, it's no surprise that many companies are "realizing tangible benefits from outsourcing specialized regulatory affairs and compliance services to expert partners who can help ensure programs minimize risk, adhere to quality and manufacturing standards, and reduce unnecessary delays," as per the report.

"The evolving regulatory framework in the pharmaceutical industry, continued focus among sponsors to streamline the pathway from idea to regulatory approval, and increasingly complex drug candidates have driven demand for outsourced compliance providers," the report states.

The authors add that, "Transaction activity in the Pharmaceutical Outsourcing industry has remained robust, with 44 transactions announced or completed year-to-date (YTD), outpacing 33 deals through YTD 2018. CROs have continued to account for the largest percentage of transaction activity (34.1 percent), followed by consulting and CDMOs, at 29.6 percent and 22.7 percent, respectively."

Of those deals, some of the biggest acquisitions of the first three quarters of the year included Permira Advisers' acquisition of Cambrex, a CDMO in the small-molecule industry, for an enterprise value of $2.5 billion; Paragon's acquisition of Catalent for $1.2 billion; and J.R. Automation's acquisition of Hitachi for $1.425 billion. ■

EDITCONNECT: E022024

VESICLES

CONTINUED FROM PAGE 32

basis, or as part of a wider range of services that would accelerate internal research and development capabilities."

Added Dr. Antonio Chiesi, CEO of Exosomics: "We believe that by implementing the nano-flow cytometry platform, we are once more leading the extracellular vesicles research field and we can offer the widest range of services to biotech/pharma and academic groups. This instrument will also allow us to further develop our own liquid biopsy pipeline, which requires the highest level of accuracy and reproducibility."

The NanoAnalyzer is designed for research use only. It is not for use in diagnostic procedures.

Established in 2012 and hosted in one of the largest and more active bio-parks in Italy, Tuscany Life Sciences, Exosomics is active in the area of liquid biopsy in cancer. After several years of research and development work and intellectual property development, it is now at commercial stage, launching its proprietary and innovative solutions into the molecular diagnostics market. Exosomics says that its distinguishing factor is the capability to isolate tumor-derived exosomes through proprietary affinity methods—thus enriching for tumor-derived proteins, DNA and RNA—and therefore significantly improving molecular diagnostics in cancer and allowing early pan-cancer screening.

"We believe that by implementing the nano-flow cytometry platform, we are once more leading the extracellular vesicles research field and we can offer the widest range of services to biotech/pharma and academic groups."

Dr. Antonio Chiesi, CEO of Exosomics

Given that tumor-derived exosomes contain biomarkers identical to those expressed on a cancer cell surface, and are poorly expressed in healthy individuals, Exosomics considers exosome-based liquid biopsy as the next generation of cancer diagnostics, which will not only complement but surpass traditional biopsy.

NanoFCM is a privately held company based in Xiamen, China, which focuses on the development of high-performance analytical instruments. It has developed a next-generation nanoparticle analysis platform, the NanoAnalyzer, based on nano-flow cytometry. The company states that it is unique in its ability to deliver comprehensive measurement (size, concentration and phenotyping) down to 10 nm to 40 nm, depending on the nature of the substrate. ■

EDITCONNECT: E022025

DMPK

CONTINUED FROM PAGE 32

and Evotec. He has a Ph.D. in toxicology from the London School of Pharmacy.

Robert Kime is another recent recruit to Sygnature's DMPK team. He joined as associate director of DMPK in November. Kime was recruited from the pharma company Grünenthal, where he was associate scientific director. Before that Kime had roles at CROs, including Quintiles. He brings important client-side experience to the team.

"Having run drug discovery projects within a pharma company using an integrated approach, I understand what a client needs from a CRO," Kime said. "My experience on both sides of the fence gives me an insight into client thinking, and what they need from us to be reassured we can do the job for them."

In addition to Dilworth and Kime, Sally Lee has joined Sygnature Discovery as a principal scientist, bringing more than 20 years of DMPK experience in both assay and project management roles. In her previous position at the AntiMicrobial Resistance Centre, Lee coordinated DMPK requests for novel antimicrobials targeting the threat of antibiotic resistance.

"As well as adding new skills and techniques to our DMPK portfolio, we are strengthening the expertise we already have. Our presence in both Nottingham and Alderley Park gives our clients access to a large pool of talented scientists and capabilities," explained Dilworth. "We aim to expand the DMPK groups in both sites to provide our clients with a harmonized and efficient service."

Sygnature now has 37 members on its DMPK team, with 24 in the Nottingham labs and another 13 in Alderley Park. Further expansion of the team is planned for this year, in order to meet growing global demand for Sygnature's DMPK capabilities.

CREDIT: SYGNATURE DISCOVERY

From left to right, recently hired Robert Kime, Clive Dilworth and Sally Lee, who boost Sygnature Discovery's drug metabolism and pharmacokinetics capabilities.

Sygnature's subsidiary, *in-vivo* pharmacology and consultancy services firm RenaSci, also added to its team in January, bolstering their kidney disease and fibrosis capabilities with the appointment of Dr. Wioletta Pijacka.

Pijacka is an *in-vivo* translational biologist with over 12 years of experience in renal and cardiovascular biology. She has worked in several scientific areas, including fetal programming in kidney disease, cardiovascular and neuroscience. Pijacka joins RenaSci from AstraZeneca, where she focused on the area of chronic kidney diseases. Prior to AstraZeneca, Pijacka was a senior research associate at the University of Bristol for more than five years, following the completion of her Ph.D. at the University of Nottingham.

"RenaSci is a world-renowned *in-vivo* pharmacology provider, so I'm obviously very excited about joining the team. Also, with RenaSci being part of the Sygnature Group, the opportunity to create synergies with Sygnature Discovery's capabilities in kidney disease and fibrosis is one I am really looking forward to; it will be an exceptional service offering," commented Pijacka.

Over the years, Pijacka has developed a unique area of research, having discovered the role of carotid bodies in hypertension and kidney diseases. Pijacka has also gained a wealth of expertise in developing fit-for-purpose animal models used in clinical translation.

"Having run drug discovery projects within a pharma company using an integrated approach, I understand what a client needs from a CRO. My experience on both sides of the fence gives me an insight into client thinking, and what they need from us to be reassured we can do the job for them."

Robert Kime of Sygnature Discovery

In her new role as a study director at RenaSci, Pijacka will be responsible for implementing and developing new *in-vivo* and *ex-vivo* models of kidney disease. First she will set up a slice model using kidneys, as well as a surgical model of kidney disease.

"We are absolutely delighted to welcome Wioletta to the RenaSci team. She brings with her specialist experience and extensive knowledge of models of kidney disease and fibrosis, which will greatly add to our existing capabilities," noted Dr. Sharon Cheetham, director at RenaSci. "We are excited in being able to expand our offering in this area and further enhancing our integration with Sygnature Discovery." ■

EDITCONNECT: E022026

BUSINESS & GOVERNMENT POLICY

BRIEFS

The handoff is complete

LONDON—GlaxoSmithKline plc (GSK) recently completed the divestment of its travel vaccines Rabipur, for the prevention of rabies, and Encepur, for the prevention of tick-borne encephalitis, to Bavarian Nordic. In keeping with the terms of the divestment agreement, Bavarian Nordic has paid GSK £308 million ($263 million) in an upfront payment, which will be followed by other milestone payments for a total consideration of up to £955 million.

"With the acquisition now completed, we can truly begin the commercial transformation of Bavarian Nordic, driven by established and proven commercial products, which along with our smallpox and monkeypox vaccine create a leading infectious disease franchise that will drive sustained profits and growth in the years ahead," said Paul Chaplin, president and CEO of Bavarian Nordic.

Determining standards for biosimilar insulin

The FDA released a draft guidance on biosimilar insulin products in late 2019 titled "Clinical Immunogenicity Considerations for Biosimilar and Interchangeable Insulin Products." The guidance details what data may or may not be required to support an argument of biosimilarity or interchangeability for an insulin product, and notes that strict standards will need to be met. In addition, beginning March 23, approved New Drug Applications for biological products will be considered licenses for the products (i.e. approved Biologics License Applications) under section 351 of the Public Health Service Act, according to a statement from FDA Commissioner of Food and Drugs Dr. Brett P. Giroir. Once an approved NDA is deemed to be an approved BLA, the product, such as an insulin alternative, can be used as a "reference product" against which a biosimilar or interchangeable product can be compared. The FDA began accepting comments on the draft guidance on Nov. 29.

IN THIS SECTION

MorphoSys and Incyte sign collaboration and license deal

Agreement focuses on tafasitamab for the treatment of B cell malignancies

BY JEFFREY BOULEY

PLANEGG, Germany & WILMINGTON, Del.—Looking to push forward MorphoSys AG's proprietary anti-CD19 antibody tafasitamab (MOR208) globally, MorphoSys and Incyte Corp. announced in January that they had entered into a collaboration and license agreement to further develop and commercialize the Fc-engineered antibody against CD19, which is currently in clinical development for the treatment of B cell malignancies.

"The global partnership with Incyte is an important step towards unlocking the full potential of tafasitamab and achieving our goal of rapidly bringing tafasitamab to patients inside and outside of the U.S.," said Dr. Jean-Paul Kress, CEO of MorphoSys. Under the terms of the deal, MorphoSys and Incyte will co-commercialize tafasitamab in the United States, while Incyte has exclusive commercialization rights outside of the country.

Continued Kress: "The combination of

DEAL CONTINUED ON PAGE 35

CREDIT: MORPHOSYS

"The combination of our strong antibody and drug development expertise partnered with Incyte's well-established hematology-oncology experience and their commercial operations in key territories has the potential to significantly broaden the tafasitamab opportunity," says Dr. Jean-Paul Kress, CEO of MorphoSys (a lab of which is pictured here).

The EMA and the U.K. after Brexit

United Kingdom withdrawal from European Union changes dynamics

BY *DDNEWS* STAFF

As the European Union (EU)-based European Medicines Agency (EMA) announced recently, the United Kingdom formally left the European Union (the process colloquially referred to as Brexit) at the end of January 2020 and will become a third country to the EU. Up to this point, the United Kingdom has been a central part of the EMA, hosting its headquarters, though that honor is now shifting to Amsterdam in the Netherlands.

A transition period began Feb. 1 and is due to end on the last day of this year. During the transition period, EU pharmaceutical law as laid out in the "Acquis Communautaire" will continue to be applicable to U.K. operations, meaning that pharmaceutical companies can continue to carry out activities in the United Kingdom until the end of the year.

Companies have until the end of December to make the necessary changes to ensure that their authorized medicines comply with EU law and can remain on the EU market. Marketing authorization holders and applicants can still be established in the United Kingdom, and qualified persons for pharmacovigilance and pharmacovigilance system master files, as well as quality control testing sites, can still be based in the country until the end of 2020.

Updated Brexit-related guidance for companies will be published shortly.

The withdrawal agreement foresees that following its departure from the EU, the United Kindgom will no longer participate

BREXIT CONTINUED ON PAGE 37

ON THE CUTTING EDGE

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

BY JEFFREY BOULEY

THIS MONTH'S roundup of recent product and service news includes an RNA Library Prep Kit from Bio-Rad Laboratories Inc., cannabis processing upgrades from Adastra Labs Holdings Ltd., a new CO_2 sensor for incubators from CO2Meter Inc., the movement of HyStem technology for the R&D market to Advanced BioMatrix, and scale-up of a novel silicon chip for synthetic biology from Evonetix Ltd.

Bio-Rad enters RNA-Seq library prep market

HERCULES, Calif.—Bio-Rad Laboratories Inc. in January announced the launch of the SEQuoia Complete Stranded RNA Library Prep Kit, which the company calls "a novel approach to RNA-Seq library preparation" that offers a "holistic view of the complete transcriptome in a simplified workflow and is compatible with a broad range of sample inputs from a variety of sample types including degraded RNA specimens."

TOOLS & TECHNOLOGY

The launch of the SEQuoia Complete Kit follows Bio-Rad's 2019 acquisition of 2D Genomics, a California Bay Area startup that developed and patented innovative enzyme technologies to improve next-generation sequencing (NGS) sample preparation, including SEQzyme, which is at the core of the SEQuoia Complete Stranded RNA Library Prep Kit. SEQzyme is said to be unique in that it couples cDNA synthesis with adapter addition in a continuous synthesis reaction, constructing sensitive and diverse

EDGE CONTINUED ON PAGE 37

DEAL

CONTINUED FROM PAGE 34

our strong antibody and drug development expertise partnered with Incyte's well-established hematology-oncology experience and their commercial operations in key territories has the potential to significantly broaden the tafasitamab opportunity. We are pleased to work with Incyte to jointly improve the lives of patients suffering from DLBCL [diffuse large B-cell lymphoma] and other devastating diseases."

Under the terms of the agreement, MorphoSys will receive an upfront payment of $750 million and, in addition, Incyte will make an equity investment into MorphoSys of $150 million in new American Depositary Shares of MorphoSys at a premium to the share price at signing of the agreement. Depending on the achievement of certain developmental, regulatory and commercial milestones, MorphoSys will be eligible to receive milestone payments amounting to up to $1.1 billion. MorphoSys will also receive tiered royalties on net sales of tafasitamab outside of the United Sates in a mid-teens to mid-twenties percentage range of net sales.

"Bringing together Incyte's expertise and MorphoSys' commitment to innovation will allow us to make tafasitamab widely available to patients with cancer, upon approval," said Hervé Hoppenot, CEO of Incyte. "We look forward to collaborating closely with the team at MorphoSys and adding tafasitamab to our portfolio of oncology candidates as part of our commitment to bringing new, advanced treatment options to patients and the clinical community around the world."

"Bringing together Incyte's expertise and MorphoSys' commitment to innovation will allow us to make tafasitamab widely available to patients with cancer, upon approval."
Hervé Hoppenot, CEO of Incyte

Both parties have agreed to co-develop tafasitamab broadly in relapsed/refractory diffuse large B cell lymphoma (r/r DLBCL), frontline DLBCL and additional indications beyond DLBCL, such as follicular lymphoma (FL), marginal zone lymphoma (MZL) and chronic lymphocytic leukemia (CLL).

Incyte will be responsible for initiating a combination study of its investigational PI3K-delta inhibitor parsaclisib and tafasitamab in r/r B cell malignancies. Further, Incyte will be responsible for leading any potential registration-enabling studies in CLL and a Phase 3 trial in r/r FL/MZL. MorphoSys will continue to be responsible for its currently ongoing clinical trials of tafasitamab in non-Hodgkin lymphoma, CLL, r/r DLBCL and frontline DLBCL. The parties will share responsibility in starting additional global trials, and Incyte intends to pursue development in additional territories including Japan and China.

MorphoSys recently submitted a Biologics License Application to the U.S. Food and Drug Administration for tafasitamab in combination with lenalidomide for the treatment of r/r DLBCL, and the FDA decision regarding a potential approval is expected by the middle of this year. The submission of a Marketing Authorization Application to the European Medicines Agency in r/r DLBCL is planned for mid-2020.

Via the online publication *Vantage*, Jacob Plieth of pharma anlaysis firm Evaluate wrote, "It's probably fair to say that biotech investors hungry for deals at the start of this week's JP Morgan healthcare jamboree were expecting something bigger than Lilly's buyout of Dermira and the licensing deal Incyte struck today for Morphosys' tafasitamab, [but the MorphoSys-Incyte] deal is not to be sniffed at. It represents the joint fifth-biggest single-project licensing transaction by up-front value—$750m—of recent times, and is an amazingly strong endorsement of an asset that still has a lot left to prove."

FierceBiotech writer Nick Paul Taylor echoed some of those sentiments by noting, "The range of therapeutic and geographic opportunities—Incyte highlighted China and Japan as new markets it wants to target—creates the potential for tafasitamab to be a significant product. For that to happen, tafasitamab needs to back up the promise it has shown to date with impressive data in studies with control arms." ■

EDITCONNECT: E022028

TARGETS ACQUIRED

A look at a few recent acquisition deals in the pharma world

BY JEFFREY BOULEY

LEADING OFF THIS COLLECTION of recent acquisition deals is news on Jan. 30 from Cambridge, U.K-based Abcam plc that it had purchased the gene-editing platform and oncology product portfolio of Milpitas, Calif.-based Applied StemCell Inc. (ASC) for life-sciences research and diagnostic markets. Abcam notes that ASC is a long-established leader in the edited cell lines market, focused on developing genome-editing technologies into novel therapeutics to advance drug discovery, and pointed out that the deal expands Abcam's cell-engineering capabilities, "adding comprehensive gene-editing capabilities and engine to drive expansion of Abcam's 'off-the-shelf' edited cell line portfolio."

CREDIT: BIONTECH

"This acquisition fits with our strategy to expand our capabilities and build our presence in the U.S. and further strengthens our immunotherapy pipeline," said Dr. Ugur Sahin, co-founder and CEO of BioNTech. "I am particularly excited about the adoptive T cell and neoantigen TCR therapies being developed by Neon, which are complementary to our pipeline and our focus on solid tumors."

Over the last 11 years, ASC has established a global reputation for solving the most difficult knock-out and knock-in cell line development challenges, according to Abcam, and they have successfully deployed their proprietary cell-editing platform to create cell lines for a broad range of diseases to support the life-science and diagnostics industries as well as to advance therapeutic drug discovery.

The transaction includes a portfolio of cell lines and the well-regarded AccuRef reference materials product line. The AccuRef product line uses ASC gene-edited cell lines to mimic cancer mutations and create biologically relevant quality control and reference standards that span over 40 cancer genes. These materials are used by laboratories and kit providers for next-generation sequencing, sanger sequencing, PCR and FISH/CISH testing.

"We are excited to expand and cement Abcam's position in the edited cell line market, bringing in one of the most widely deployed and technically successful cell engineering platforms into the Abcam family," said Cheri Walker, senior vice president of corporate development at Abcam. "The cell line market is in the early stages of development as a research tool, where the ready provision of more choice, with the right gene targets in the right cell lines, will allow the market to rapidly expand."

Abcam will expand the ASC platform to become its discovery engine for developing novel edited cell lines, building upon the extensive range of knock-out cell lines acquired through the Edigene transaction in 2019. Ready-made knock-out cell lines play a significant role in the study and understanding of biological pathways and disease models.

Commented Ruby Tsai, co-founder and chief scientific officer of Applied StemCell: "Following our strategic decision to focus on stem cell and derivative service and products for both research and therapeutic applications, we are pleased to be transitioning our oncology-focused services and products to the global team at Abcam. As recognized industry leaders in the provision of biologic reagents and tools, Abcam is ideally placed to provide expert support to our global user-base."

BioNTech to acquire Neon and strengthen position in T cell market

MAINZ, Germany & CAMBRIDGE, Mass.—BioNTech and Neon Therapeutics Inc. have entered into a definitive merger agreement under which BioNTech will acquire Neon in an all-stock transaction valued at approximately $67 million, combining two companies "with a common culture of pioneering translational science and a shared vision for the future of cancer immunotherapy."

Neon is a biotechnology company developing novel neoantigen-based T cell therapies. Upon closing, it will operate as a subsidiary of BioNTech, a global clinical-stage biotechnology company focused on patient-specific immunotherapies for the treatment of cancer and other serious diseases.

"This acquisition fits with our strategy to expand our capabilities and build our presence in the U.S. and further strengthens our immunotherapy pipeline," remarked Dr. Ugur Sahin, co-founder and CEO of BioNTech. "I am particularly excited about the adoptive T cell and neoantigen TCR therapies being developed by Neon, which are complementary to our pipeline and our focus on solid tumors."

Added Hugh O'Dowd, CEO of Neon: "We are very proud of all we have accomplished since we founded Neon, and look forward to joining forces with BioNTech to continue to build a business that provides life-changing immunotherapy products to patients battling a variety of cancers."

Neon has deep expertise in the development of neoantigen therapies, with both vaccine and T cell capabilities. Neon's most advanced program is NEO-PTC-01, a personalized neoantigen-targeted T cell therapy candidate consisting of multiple T cell populations targeting the most therapeutically relevant neoantigens from each patient's tumor. Neon is also advancing a precision T cell therapy program targeting shared neoantigens in genetically defined patient populations. The lead program from this approach, NEO-STC-01, is a T cell therapy candidate targeting shared RAS neoantigens. In addition, Neon has assembled libraries of high-quality TCRs against various shared neoantigens across common human leukocyte antigens.

Neon's pipeline is underpinned by its platform technologies, including RECON, its machine-learning bioinformatics platform, and NEO-STIM, its proprietary process to directly prime, activate and expand neoantigen-targeting T cells *ex vivo*.

The transaction was unanimously approved by both BioNTech's and Neon's boards of directors. The transaction, which is expected to close during the second quarter of 2020, is subject to approval of Neon's shareholders and the satisfaction of customary closing conditions.

CREDIT: RECIPHARM

Swedish company Recipharm (the Wasserburg, Germany, site of which is pictured here) recently gained clearance from German regulators to acquire Consort Medical plc.

Recipharm receives clearance from Germany to acquire Consort Medical

STOCKHOLM—Toward the end of last year, Recipharm AB set out the full terms and conditions of its recommended cash offer to acquire the entire issued and to-be-issued share capital of Consort Medical plc. The offer remained subject to, among other things, approval from the competition authority in Germany, which Recipharm received in early December.

Completion of the offer remains subject to other outstanding conditions, such as the Irish antitrust condition and the acceptance condition, as set out in the offer document.

Recipharm is a contract development and manufacturing organization in the pharmaceutical industry employing almost 7,000 employees, offering manufacturing services of pharmaceuticals in various dosage forms, production of clinical trial material and active pharmaceutical ingredients, as well as pharmaceutical product development.

Waters to acquire Andrew Alliance

MILFORD, Mass.—Mid-January brought news that Waters Corp. had entered into a definitive agreement to acquire Andrew Alliance, an innovator in specialty laboratory automation technology, including software and robotics. Andrew Alliance's cloud-native software platform and modern interface dramatically improve the use of automation technology, enabling more scientists to realize the advantages of repeatability and performance for both routine and complex laboratory workflows.

"The acquisition of Andrew Alliance broadens our technology portfolio to include advanced robotics and software that will positively impact our customers' workflows across pharmaceuticals, life-sciences and materials science markets," commented Chris O'Connell, chairman and CEO of Waters. "This move also demonstrates Waters' commitment to deploy capital to growth-oriented acquisitions that reinforce our specialty strategy and enhance our core business."

Waters

THE SCIENCE OF WHAT'S POSSIBLE.®

Waters Corp. plans to acquire Andrew Alliance, an innovator in specialty laboratory automation technology.

Andrew Alliance has approximately 40 employees in Switzerland, France and the United States.

"We are thrilled to join the Waters family," said Piero Zucchelli, CEO of Andrew Alliance. "We have found the right partner to bring our vision of connected laboratories to life. Waters' combination of instruments and chemistries will help us accelerate the delivery of our innovative software and hardware technologies to customers as mass spectrometry increasingly moves into the hands of more and more users." ■

EDITCONNECT: E022031

Bio-Rad's SEQuoia Complete Stranded RNA Library Prep Kit.

EDGE

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libraries compatible with Illumina NGS platforms.

"We are pleased to add the technologies of 2D Genomics to Bio-Rad's portfolio of enabling genomic solutions," said Annette Tumolo, president of the Life Science Group at Bio-Rad. "We believe the SEQuoia Complete Stranded RNA Library Prep Kit will provide us a strong start as we step into the RNA sequencing preparation market. The kit's ability to construct robust and complex libraries, including both short and long RNAs, can result in tremendous advancements in research, including the discovery of biologically relevant biomarkers beyond just mRNA."

Adastra Labs' cannabis processing equipment.

Adastra Labs installs cannabis processing equipment

LANGLEY, British Columbia—Adastra announced at the end of January the installation of its cannabis processing equipment at their facility in Langley. In early December, Adastra accepted the delivery of a GMP-compliant Series 140 supercritical CO_2 extraction system and post-processing equipment from extraktLAB, a brand of United Science LLC.

Completion of the extraction equipment and post-processing equipment installation will allow Adastra to create what it calls "high-value cannabis extract products" from cannabis plant material immediately following the issuance of a Standard Processing License from Health Canada. The Series 140 extractor and associated post-processing equipment is reportedly capable of efficiently and safely removing THC and CBD from over 58,000 kg of cannabis biomass per year without the use of hydrocarbon solvents.

CO2Meter launches new incubator sensor for life sciences

ORMOND BEACH, Fla.—Early this year, CO2Meter, a manufacturer of gas detection and monitoring solutions, released a new MicroSENS Hightemp IR CO_2 Incubator Sensor for incubators that monitors and controls the environments for cell cultures, tissue samples and bacteria growth patterns. The "highly anticipated" sensor reportedly will provide reliable and highly accurate gas measurement in incubators without having to remove the sensor during high-temperature sterilization cycles.

"We decided to partner with Micro-Hybrid Electronic GmbH because of their 20-plus years of experience in the manufacturing of IR components and measuring systems. We know that scientists, researchers and laboratory technicians worldwide need a proven, reliable and accurate means of precisely controlling their chambers' conditions, all while eliminating contamination," noted Travis Lenander, CEO of CO2Meter. "The MicroSENS Hightemp sensor will set a new standard in the market because of its ability to accurately measure the precise CO_2 concentration and to compensate temperature and humidity influence, while also being left in place during high-temperature sterilization cycles. Our field testing partners have told us that the ability to leave the MicroSENS Hightemp IR CO2 Incubator Sensor in place during sterilization is an enormous time and cost savings to their laboratories."

CO2Meter's MicroSENSE HighTemp IR CO2 Incubator Sensor.

Added Josh Pringle, vice president of business development for CO2Meter: "We strive to develop sensors and products that solve a customer's needs. These solutions fill a 'gap' in the market that we can then capitalize on and sell in to. The CO2Meter team takes pride in our ability to identify and become experts in specific markets, allowing us to market and sell from a position of knowledge rather than being outsiders looking in."

Advanced BioMatrix acquires HyStem from Lineage

CARLSBAD, Calif.—Advanced BioMatrix recently acquired the HyStem line of products from Lineage Cell Therapeutics. HyStem kits are based on innovative thiolated hyaluronic acid technology, allowing researchers to create customizable 3D hydrogels for culturing cells whose natural environment is rich in hyaluronic acid.

This acquisition includes the transfer of technology, intellectual property, know-how and assets for the manufacturing and sale of HyStem products for research and development purposes.

"The HyStem family of hyaluronan-based hydrogels is highly complementary and fits perfectly into our catalog of innovative 3D matrices and hydrogels," said David Bagley, president of Advanced BioMatrix. "This acquisition will further strengthen the Advanced BioMatrix position as an industry leader in extracellular matrices and provide a broader range of high-quality products to our customers."

Evonetix collaborates with imec to scale up third-generation DNA synthesis platform

CAMBRIDGE, U.K. & LEUVEN, Belgium—Evonetix, a synthetic biology company developing a desktop platform for scalable, high-fidelity and rapid gene synthesis, has partnered with imec, a research and innovation hub active in the fields of nanoelectronics and digital technologies, to increase production of Evonetix's proprietary microelectromechanical systems (MEMS)-based silicon chips, enabling the platform to be manufactured at a commercial scale. The novel silicon chip is a key component of Evonetix's desktop DNA platform which, once fully developed, will facilitate and enable the rapidly growing field of synthetic biology.

Evonetix's technology utilizes a silicon chip, made by MEMS processing, that controls the synthesis of DNA at many thousands of independently controlled reaction sites or "pixels" on the chip surface in a highly parallel fashion. Following synthesis, strands are assembled on-chip into double-stranded DNA in a process that identifies and removes errors, enabling accuracy, scale and speed that is several orders of magnitude better than conventional approaches. Under the terms of the collaboration, imec will work with Evonetix to scale up manufacturing of the MEMS technology on 8-inch silicon wafers, enabling Evonetix to supply customers in volume. imec is able to leverage its experience in manufacturing silicon for life-sciences applications to transfer the novel Evonetix process to their foundries and to manage further expansion in volume.

"With the support of imec, a world-renowned leader in microchip technology, we will be able to optimize our highly parallel desktop platform for commercial supply," stated Dr Matthew Hayes, chief technology officer at Evonetix.

According to Peter Peumans, vice president of the Life Science Technologies operation at imec: "We have extensive practical knowledge of chip design and technology, which we use to help develop innovative tools for the life sciences and pharma R&D. Evonetix has developed an innovative approach that integrates physics and biology to enable the production of high-fidelity long DNA in a highly parallel fashion. We are eager to contribute to their success using our nanotechnology capabilities." ■

EDITCONNECT: E022029

BREXIT

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in EU institutions and their decision-making. For the EMA, this means that as of Feb. 1, no one who represents the United Kingdom, or is appointed or nominated by the country, can participate in meetings of EMA's scientific committees, working parties or the agency's management board.

Noted the EMA in their announcement: "The agency would like to thank all U.K. delegates and experts for their involvement in the scientific and regulatory activities of EMA since its establishment 25 years ago. Their professionalism and commitment have contributed greatly to the development and functioning of the strong and efficient system for medicines regulation that we have in the EU today." ■

EDITCONNECT: E022030

Late-Breaking News

NEWS ITEMS THAT ARRIVED TOWARD THE TAIL END OF THIS ISSUE'S PLANNING AND PRODUCTION PROCESS

Purdue says Wuhan virus genetically similar to SARS, works toward therapeutics

WEST LAFAYETTE, Ind.—Purdue University scientists Andrew Mesecar, the university's Walther Professor in Cancer Structural Biology and head of the Department of Biochemistry, and Arun Ghosh, the Ian P. Rothwell Distinguished Professor of Chemistry, have been working to develop both oral medicines and vaccines to fight coronaviruses. They are now working to test their potential drug molecules on the new SARS-like Wuhan coronavirus.

Although no potential drug identified now will be helpful in the current outbreak, the researchers hope that they can use the discoveries they make with the current virus to better mitigate future outbreaks.

In the case of these Purdue scientists, they are developing a drug that works by blocking two of the coronavirus enzymes (proteases), thus preventing it from replicating. Moreover, this is not unlike what they have seen before, which may make things a little easier, with Mesecar noting, "The drug targets we've identified are over 95-percent identical to the enzyme targets we saw on the SARS virus."

SARS, or severe acute respiratory syndrome, was first discovered in Asia in February 2003, and the outbreak lasted approximately six months as the disease spread to more than two dozen countries in North America, South America, Europe and Asia before it was stopped in July 2003. But technology and know-how have improved since then.

"In 2002 when the SARS outbreak happened, it took months to get to the point where we are now," Mesecar said. "With this outbreak, scientists were able to isolate the virus and sequence the genome in less than two weeks. One week later, an additional 20 genomes were available. In another week or two, we'll be able to begin to see if the virus is mutating."

CREDIT: PURDUE UNIVERSITY

Researchers at Purdue University are working on potential therapeutics that could fight the current Wuhan coronavirus and any future variants or even new types of coronavirsuses.

In identifying drug targets on the coronavirus, they take an antiviral approach similar to what Ghosh used to develop the anti-HIV drug darunavir, which is sold under the brand name Prezista.

"MERS virus and the SARS virus are more different genetically," Mesecar explains. "But the Wuhan virus is genetically almost identical to the SARS virus and, therefore, it is expected to look and act nearly the same."

However, the future of a drug like this is uncertain, given the intermittent nature of these outbreaks and the relatively small market for drugs compared to addressing chronic diseases, which means pharma companies have less incentive for development.

Mesecar is working to set up a rapid-response system of scientists that could quickly develop drugs during future outbreaks caused by genetic variants of the coronavirus. The goal is to have a library of FDA-approved or almost-approved compounds that have been predetermined to work on specific coronaviruses so that when an outbreak appears, medicines can be produced and distributed quickly. ■

"In 2002 when the SARS outbreak happened, it took months to get to the point where we are now. With this outbreak, scientists were able to isolate the virus and sequence the genome in less than two weeks."

Andrew Mesecar of Purdue University

Adapted from a Purdue University article online by Steve Tally.

Moderna gets funding for mRNA vaccine against novel coronavirus

CAMBRIDGE, Mass.—Moderna Inc., a clinical-stage biotech focused on messenger RNA (mRNA) therapeutics and vaccines, and the Coalition for Epidemic Preparedness Innovations (CEPI) have announced a collaboration to develop an mRNA vaccine against the novel coronavirus (2019-nCoV) that seems to have originated in Wuhan, China.

Per the agreement, Moderna will manufacture an mRNA vaccine against 2019-nCoV, funded by CEPI. The Vaccine Research Center of the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH), collaborated with Moderna to design the vaccine. NIAID will conduct IND-enabling studies and a Phase 1 clinical study in the U.S.

Over the past four years, Moderna has had six positive Phase 1 clinical readouts in its prophylactic vaccines modality and moved two additional programs into development. Moderna's technology platform, fully integrated manufacturing site and development experience, combined with a multiyear relationship with the NIH, allows for the rapid identification and advancement of a vaccine candidate against 2019-nCoV.

"Moderna's commitment to global public health is aligned with CEPI's vision of creating a world in which epidemics are no longer a threat to humanity," said Dr. Richard Hatchett, CEO of CEPI. "We are pleased with the pace of our combined response to the emerging threat of the novel coronavirus. Through our partnership with Moderna and the NIH, we hope to speed the development of a vaccine against the coronavirus and help to alleviate the burden of disease."

"Advances in global public health require the collective effort of public-private partnerships—no organization can act alone."

Stéphane Bancel, CEO of Moderna

Added Stéphane Bancel, CEO of Moderna: "We believe our mRNA vaccine technology offers potential advantages in the speed of development and production scalability, which positions Moderna to potentially develop a vaccine against coronavirus, 2019-nCoV. Advances in global public health require the collective effort of public-private partnerships—no organization can act alone. We are honored to be supporting NIH and CEPI in their mission to identify a potential vaccine to prevent infection. It is impressive that CEPI was able to commit to this grant in a matter of days. We are thankful for the financial support from CEPI and the multiyear scientific collaboration we have with the NIH." ■

For additional coronovirus news, go to www.ddn-news.com and use search window at the top to search for the code E022040.

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[i] Based on independent third-party testing for Model MDF-DU702VHA-PA at time of publication. ENERGY STAR test results for submitted products can be compared for performance across the competitive market. Results published at www.energystar.gov. See Certification Numbers 4788723268, 4788321237, 4787624502.
[ii] MDF-DU901VHA-PA, 115V

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