ProMIS targets Parkinson’s disease—Alzheimer’s is next

Company has high hopes for antibody candidates targeting toxic oligomers

BY KRISTEN SMITH
MISSISSAUGA, Ontario—ProMIS Neurosciences Inc. recently announced that they have identified several potential antibody therapeutic candidates aimed at selectively targeting toxic oligomers of the protein \( \alpha \)-synuclein, which is considered a root cause of Parkinson’s disease (PD) and is linked to Alzheimer’s disease (AD) and amyotrophic lateral sclerosis (ALS) as well. While the root causes of these related neurodegenerative diseases remain disputed, several studies definitively implicate toxic oligomers in the development and progression of PD.

ProMIS began looking at the toxic oligomer based on research linking it to Alzheimer’s disease. Alzheimer’s drug developers have predicated most new treatments on the long-held “amyloid hypothesis.” This popular theory—with roots that date back more than 100 years—held that amyloid beta, a naturally occurring substance that forms clumps in the brain, could become dangerous for some people as they age, much like how a normal cell might become cancerous. The amyloid hypothesis held that sometimes these clumps—commonly called “plaques”—would strangle brain cells, leading to their death and eventually, disease onset. Drug developers erroneously believed that by targeting plaque in the brain, they could develop a therapy that would halt Alzheimer’s disease, but 25 years of drug development were

Recruitment in the digital age

Study reveals that ‘traditional digital advertising rules don’t apply’ in clinical trial recruitment

BY JEFFREY BOULEY
RALEIGH, N.C.—Syneos Health, a fully integrated biopharmaceutical solutions organization, in mid-October released a study that it says provides real-world patient insights into the effectiveness of digital advertising to speed clinical trial recruitment. That research highlighted by the study—presented at Digital Pharma East in Philadelphia—finds that traditional digital advertising rules don’t necessarily apply well to recruitment efforts for clinical trials. The study was conducted online with 432 patients in the United States who had epilepsy and migraine—two conditions with active late-phase pipelines, Syneos notes—and was aimed at helping digital marketers

Themis pursues oncolytic virotherapies with Max-Planck

Company plans to expand measles vector immunomodulation portfolio into oncology indications

BY MEL J. YEATES
VIENNA, Austria—In early October, Themis Bioscience publicized a license agreement with Max-Planck-Innovation GmbH, the technology transfer agency of the Max Planck Society in Germany, granting Themis exclusive worldwide license to develop, manufacture and commercialize therapies based on an oncolytic measles virus platform that was jointly

Strategies for using digital advertising to recruit patients for clinical trials may require slightly different strategies than for other applications of such online methods, according to new research by Syneos Health.
With hundreds of known cancer types and a steady increase in the incidence of cancer worldwide, researchers need a diverse range of innovative technologies to help unravel the complexities of the disease. Our cancer research solutions support your research and discovery, wherever it leads – from genomics to cell-based analysis to animal and tissue imaging – and can help you translate your findings into more effective treatments. Cancer is a complex story – and now you have the tools to help you understand it.

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Mental health future looking brighter for patients

LONDON—Just in time for World Mental Health Day 2018 on Oct. 10, data and analytics company GlobalData noted that while the treatment of mental health disorders has improved drastically and the stigma associated with these indications has been stripped away considerably, there remains a long way to go to address the gaps in the market.

As the firm notes, “Mental health has a huge social and economic burden on patients, with one in six adults reported to have a common mental health disorder.”

Over the last decade, there have been several outreach and educational programs that have helped to reduce the stigma surrounding these disorders, and patients are now receiving more adequate care. However, there is still more that can be done, noted Rahael Maladwala, a pharma analyst at GlobalData: “Pharmaceutical companies are now seeing these gaps in the market and commissioning research into the etiology and pathophysiology of these indications to better understand how they work and developing drugs that target the root cause of these diseases.”

Clinical research in the form of drugs is not the only trend that is being used to address the gaps in the market, according to Maladwala, who added, “This is where the creativity of pharmaceutical companies comes into play. There have been several digital approaches that are being trialed to help meet some of the unmet needs for some of these indications; examples of this include Otsuka’s use of a digital sensor in a pill used for schizophrenia treatment to improve compliance, Takeda and Cognition Kits have partnered to develop an app synced to a piece of wearable technology which monitors MDD patients, and several companies are using artificial intelligence to help identify potential drug targets for these disorders. The use of technology is helping to revolutionize patient care, right from drug discovery to drug delivery.”

A barricade to increased biosimilar use for rheumatoid arthritis

LONDON—Although biosimilars have become an increasingly important force within the rheumatoid arthritis (RA) treatment landscape, they have experienced an unexpectedly slow uptake in many geographical markets in comparison to traditional generic drugs, says GlobalData, a leading data and analytics company.

GlobalData conducted a survey among high-prescribing rheumatologists from the United States, the EU (France, Germany, Italy, Spain and the United Kingdom), Japan and Australia, and found that biosimilar prescription rates remain low outside of the EU.

“The survey results revealed that biosimilar prescription is most prolific in the EU. While 69 percent of physicians from the EU reported prescribing biosimilars to at least half of their RA patients, less than 25 percent of physicians in the U.S., Japan and Australia prescribed biosimilars at these rates,” explained Dr. Rose Joachim, a pharma analyst at GlobalData. “This highlights the success of efforts to increase biosimilar usage in the EU and suggests the presence of some serious roadblocks to the uptake of biosimilars in the U.S., Japan and Australia.”

Survey results and interviews with key opinion leaders conducted by GlobalData suggest that the main impediments to biosimilar adoption in the United States are the limited number of marketed biosimilars (only infliximab biosimilars are currently available), an ambiguous regulatory environment and unfavorable coverage by insurance providers due to contracting agreements.

Joachim continued: “Although the issue of market access might also apply to Australia and Japan, it is unlikely that this completely justifies the surveyed physicians’ lack of biosimilar usage. In comparison to RA CONTINUED ON PAGE 4
Sector trends and metrics in regenerative medicine

WASHINGTON, D.C.—In August, the Alliance for Regenerative Medicine (ARM) released a quarterly data report offering an in-depth look at cell therapy, gene therapy, tissue engineering and broader global regenerative medicine sector trends and metrics in the second quarter and first half of 2018. By further curating information provided by ARM’s data partner Informa, the report details industry-specific statistics compiled from more than 857 cell therapy, gene therapy, tissue engineering and other regenerative medicine companies worldwide, including total financings, partnerships and other deals, clinical trial information, key clinical data events and current legislative and regulatory priorities.

“There has been a tremendous amount of forward momentum during the first half of this year, both clinically and commercially,” said Janet Lynch Lambert, ARM’s CEO. “We’re excited for the continued growth of the regenerative medicine sector, and what it means for patients worldwide.”

Highlighted findings from the Q2 2018 data report include:

• Globally, companies active in gene and cellular therapies and other regenerative medicines raised more than $4.1 billion in the second quarter of 2018, a 164-percent increase from Q2 2017. The report also includes financial data broken out by technology type and financing type.
• There were 977 clinical trials underway worldwide at the close of the second quarter of 2018, with more than 54 percent of those in oncology and nearly 10 percent in cardiovascular disorders. The report also includes figures on clinical trials by phase and indication, as well as by technology type.
• ARM will continue to update this information through new reports to be released after the close of each quarter, tracking sector performance, key financial information, clinical trial numbers and clinical data events.

A boon for orphan and rare dermatology products?

LONDON—The global orphan and rare dermatology premium products market is expected to grow rapidly from $1.64 billion in 2017 to $6.07 billion in 2024 at a compound annual growth rate of 20.5 percent, according to business intelligence provider GBI Research.

The company’s report, titled “Global Orphan and Rare Dermatological Drugs Market to 2024,” identifies the changing trends in the orphan and rare dermatology drugs market, with particular focus on systemic sclerosis (scleroderma), alopecia, epidermolysis bullosa, pemphigus vulgaris, vitiligo and cutaneous lupus erythematosus.

“Many orphan and rare dermatology disorders are associated with significant quality of life impairments, particularly if the disease is insufficiently controlled,” noted Philippa Salter, an analyst for GBI Research. “However, the current therapeutic market is a highly generalized therapy area and therefore small, but this is set to change as many new products will enter the market during the forecast period, including treatments for diseases that currently have no effective treatment options.”

The number of companies with a market share in the orphan and rare dermatology therapy area is expected to more than double over the forecast period, according to GBI Research.

Salter explains: “Many of the companies which are entering the orphan and rare dermatology market over the forecast period are smaller companies with more specialized product portfolios. In 2017, only one company was generating more than 10 percent of its overall revenue from the orphan and rare dermatology therapy area. However, by 2024 there will be several companies generating more than 85 percent of their revenue from the therapy area.”

GBI Research’s report also states that pipeline innovation is moving toward addressing the significant unmet need for more efficacious and safer treatment options that target the underlying causes of disease as opposed to managing the symptoms.

“Across orphan and rare dermatological diseases, there is a strong need for innovation and development of effective disease-modifying drugs. This is reflected by the pipeline of 262 active products for orphan and rare dermatology diseases, which is reasonably large considering how rare most of the disorders are,” concluded Salter. «

“Across orphan and rare dermatological diseases, there is a strong need for innovation and development of effective disease-modifying drugs. This is reflected by the pipeline of 262 active products for orphan and rare dermatology diseases, which is reasonably large considering how rare most of the disorders are,” concluded Salter. «

A boon for orphan and rare dermatology products?
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Repurposing for neglected diseases

Data collection of existing small-molecule drugs could expedite potential therapies

**BY ILENE SCHNEIDER**

LA JOLLA, Calif.—Scientists at Calibr, a non-profit drug discovery division of Scripps Research, are using an extensive library of more than 12,000 small-molecule drugs deemed appropriate for direct use in humans to help researchers to repurpose drugs for treating a variety of illnesses. The ReFRAME (Repurposing, Focused Rescue and Accelerated Medchem) drug repurposing collection, which was compiled using widely used commercial drug databases (Clarivate Integrity, GVK Excelra GoStar and Citeline Pharmacopoeia), offers hope for treating diseases that kill millions worldwide.

Calibr researchers also mined patent filings for food drug candidates that are not yet available on these databases but appear to be potential therapies for diseases other than their original indications. Calibr then launched a campaign to garner physical samples of the compounds. They bought approximately 7,000 compounds and synthesized roughly 5,000 others. The project, which included 500 chemists over an 18-month period, is still ongoing. It has enabled Calibr to identify a host of unique compounds that have never been collected in one place and make them more readily available to researchers.

“The idea came from an over-arching concept that existing drugs could be put together to maximize the potential of drugs that had already been tested, saving time and cost,” explained Dr. Arnab Chatterjee, vice president of medicinal chemistry at Calibr and lead researcher on the project. “The idea of ReFRAME is to democratize compound screening for biologists. It is available at no cost to them. The only requirement is that they make data publicly available. We provide guidance on data analysis.”

Dr. Pete Schultz, president and CEO of Scripps Research and Calibr and a lead researcher on the ReFRAME project, added, “ReFRAME takes the concept of accelerating impact on patients through repurposing existing drugs to a new level, offering great promise in the fight against neglected diseases.”

**THE PROMISE OF RETINOIC ACID SIGNALING**

Research team publishes research on the anticancer effects of retinoic acid on cancer stem cells

**BY KELSEY KAUSTINEN**

WILMINGTON, Del.—Cancer researchers at the Helen F. Graham Cancer & Research Institute’s Center for Translational Cancer Research at Christiana Care Health System have highlighted aldehyde dehydrogenase (ALDH) as a biomarker for normal and malignant colon stem cells, further and found that as a part of the retinoic acid signaling pathway, it is functional in stem cells.

The researchers believe that by modifying these peptides to enhance their antimicrobial activity, they may be able to develop synthetic peptides that could be used as antibiotics.
potential for finding much-needed therapies more quickly and cost-effectively. The drugs we’ve assembled in ReFRAME have already been shown safe in humans, making them an incredibly valuable resource for tackling areas of urgent unmet medical need, especially neglected tropical diseases.

Thanks to the ReFRAME initiative, two FDA-approved drugs—one to treat tuberculosis and another to treat the parasite Cryptosporidium spp., a key cause of severe diarrhea—have moved from concept to clinical trials in a few years, instead of much longer timelines that often characterize new drug development. The initial drugs identified for possible repurposing using ReFRAME were the leprosy drug clofazimine and the arthritis drug auranofin. Calibr is working with the University of Washington, which is sponsoring a Phase 2A clinical trial in Malawi, and the Bill and Melinda Gates Foundation to study the safety, tolerability, pharmacokinetics and efficacy of clofazimine for treating cryptosporidiosis in HIV-positive patients. The other drug, Auranofin, is being tested for treating tuberculosis in a clinical trial taking place in South Africa.

Calibr researchers also used ReFRAME to identify two other compounds that seemed effective against Cryptosporidium spp., as reported in the Proceedings of the National Academy of Sciences. Using the institute’s high-throughput screening facility, the researchers tested all 12,000 compounds against Cryptosporidium. Only one drug, nitazoxanide, which is not highly potent and not effective in patients with compromised immune systems, is approved for treating Cryptosporidium infection. There is little other drug discovery research on it due to a lack of commercial interest, but repurposing can change that.

Calibr researchers hope to be involved in facilitating repurposed therapies for other infectious diseases in the developing world. They have created an open-access data portal (https://ReFRAMEdb.org) to share the results of their ReFRAME screening experiments with other researchers, to encourage additional follow-up and maximize the impact of the screening collection. Chatterjee concluded, “Our emphasis is to enable scientists working on neglected diseases to have access to molecules. They are sent to all parts of the world and provide great value to places with no commercial interest as well as places where there is. The key goal is to put drug data resources, mechanisms of action and indications in a public portal where they are available to researchers free of charge, as well as to provide the actual molecules. While they are of great value to everyone, they are especially useful to people who would not otherwise have access to them.”

“The idea of ReFRAME is to democratize compound screening for biologists. It is available at no cost to them. The only requirement is that they make data publicly available. We provide guidance on data analysis.” Dr. Arnab Chatterjee, vice president of medicinal chemistry at Calibr

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“New understanding of amyloid demands a version 2 of the amyloid hypothesis,” says Dr. Elliot Goldstein, president and CEO of ProMIS (a lab of which is pictured here). “We now know there are several kinds of amyloid in the brain, but only one form is toxic, the toxic oligomer. This understanding is facilitating a radical shift in AD drug development, with a new generation of drug development efforts that target the toxic oligomer.”

ProMIS launched their Parkinson’s program because significant data also implicates the toxic oligomer for PD as well as for ALS. For Parkinson’s, they are targeting the toxic oligomer that derives from alpha synuclein, a naturally occurring protein. Despite broad evidence linking the toxic oligomer to neurodegenerative diseases, the challenge has been how to selectively target it for antibodies. The toxic oligomer is a highly unstable shape-shifter, making it very difficult to isolate. ProMIS applied its thermodynamic, computational discovery platform—ProMIS and Collective Coordinates—to predict novel targets known as disease-specific epitopes on the molecular surfaces of several proteins.

“Using our unique discovery platform, we were able to identify several novel targets displayed on toxic oligomers of α-synuclein and generate antibody candidates capable of protecting brain neurons against toxic oligomers in vitro,” stated ProMIS Executive Chairman Eugene Williams. “We now look forward to further validation and selection of the most promising candidates to move forward in development for PD. We see our emerging Parkinson’s disease program as an ideal pharma partnering opportunity.”

Working with the French contract research organization Neuron Experts, they investigated the neuroprotective effect of ProMIS’ antibodies on rat primary dopaminergic neurons injured by exposure to toxic oligomers of α-synuclein, an in-vitro model of PD. In the test, several ProMIS antibodies that selectively target toxic oligomers of α-synuclein significantly blocked the death of neurons induced by these oligomers.

Commenting on these results, Goldstein stated: “We feel our patented discovery platform represents the future of drug development for neurodegenerative diseases. It marries physics with medicine, granting us the unique ability to light up new targets on the toxic oligomer, test and validate hundreds of antibody drug candidates against these targets, and then rapidly progress the strongest candidates across the finish line.”

Using their precision medicine approach, ProMIS is developing novel antibody therapeutics for AD, ALS and PD. They also hope the technique can eventually be applied to neurodegenerative diseases in general, spinal muscular atrophy, Huntington’s disease and other dementias, such as Lewy Body dementia, frontotemporal dementia and prion disease. They also see an opportunity to explore the platform’s potential in chronic, sports-related head trauma, called chronic traumatic encephalopathy.

While the latest release focuses on the progress ProMis has made looking at Parkinson’s, they intend to aggressively pursue a treatment for Alzheimer’s using the platform. According to Goldstein, they intend to look at other potential AD culprits as well.

“Our long-term goal is to develop therapies that pack a one-two punch for AD and ALS,” he noted. “Regarding AD, we know that toxic oligomers of the protein Tau also play a causal role in disease progression; we’ll target Tau next.”

The real question is what is the difference between a cancer stem cell and a normal stem cell? “We need our normal stem cells for replacing our tissues, renewing our tissues for wound healing, so we really don’t want to damage the normal stem cells in our body, but we really want to kill or eliminate the cancer stem cells in order to kill the cancer.”

Building off of previous exploration, in which Boman’s lab had highlighted aldehyde dehydrogenase (ALDH) as a biomarker for normal and malignant colon stem cells, the scientists looked into ALDH further and found that as a part of the RA signaling pathway, it is functional in stem cells. Specifically, “We discovered that the retinoic acid or RA signaling pathway acts to induce differentiation of colon cancer stem cells and reduce cancer stem cell overpopulation, which puts the brakes on the primary mechanism that drives colon cancer development,” Boman explained.

The ability of retinoic acid signaling to inhibit colon cancer is a result of a decrease in ALDH-positive colon cancer stem cells, the team discovered. In addition, retinoic acid leads to increased differentiation of cancer stem cells, which in turn decreases their ability to self-renew and blocks cell proliferation, which is a strong advantage given cancer’s unregulated replication.

Based on the hypothesis that retinoid drugs could enable them to harness this approach and selectively target cancer stem cells, Boman and his colleagues tested all-trans retinoic acid (ATRA), a retinoic acid derivative. In studies of other cancer types, ATRA has proven capable of reducing the ability for self-renewal in cancer cells. In this work, it was found to down-regulate gene expression of the ALDH stem cell biomarker, reduce stem cell renewal and inhibit tumor growth. As noted in the Oncotarget paper, “Disregulation of RA signaling in colonic [stem cells] likely contributes to overpopulation of ALDH+ [stem cells] and [colorectal cancer] growth.”

“Dr. Boman presents us with a broader view into the origins of colorectal cancer at the cellular and molecular level,” remarked Dr. Nicholas J. Petrelli, Bank of America endowed medical director of Christiana Care’s Helen F. Graham Cancer Center & Research Institute. “His work highlights the mission of the Center for Translation- al Cancer Research to hasten discoveries from bench to bedside, and draws us even closer on the path to targeted therapies that can improve survival and quality of life for patients with drug-resistant, advanced colorectal cancer.”

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MIT
CONTINUED FROM PAGE 6
against drug-resistant bacteria.

“These peptides really constitute a great
template for engineering. The idea now is to
use synthetic biology to modify them further
and make them more potent,” says Cesar de
la Fuente-Nunez, an MIT postdoc and Arec-
ces Foundation Fellow, and one of the senior
authors of the paper.

Other MIT authors of the paper, which
appears in the Jan. 20 issue of the journal
ACS Synthetic Biology, are Timothy Lu, an
associate professor of electrical engineering
and computer science and of biological engi-
neering, and Marcelo Der Torossian Torres,
a former visiting student.

Antimicrobial peptides, which are found
in nearly all living organisms, can kill many
microbes, but they are typically not pow-
erful enough to act as antibiotic drugs on
their own. Many scientists, including de la
Fuente-Nunez and Lu, have been exploring
ways to create more potent versions of these
peptides, in hopes of finding new weapons
to combat the growing problem posed by
antibiotic-resistant bacteria.

In this study, the researchers wanted to
explore whether other proteins found in the
human body, outside of the previously known
 antimicrobial peptides, might also be able to
kill bacteria. To that end, they developed a
search algorithm that analyzes databases of
human protein sequences in search of simi-
larities to known antimicrobial peptides.

“We have patterns
that we know are
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and finds patterns
that look similar to
what we know makes
up a peptide that
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Cesar de la Fuente-
Nunez of MIT

“It’s a data-mining approach to very
easily find peptides that were previously
unexplored,” de la Fuente-Nunez says. “We
have patterns that we know are associated
with classical antimicrobial peptides, and
the search engine goes through the data-
base and finds patterns that look similar to
what we know makes up a peptide that kills
bacteria.”

In a screen of nearly 2,000 human pro-
teins, the algorithm identified about 800
with possible antimicrobial activity. In
the recent paper, the research team focused
on the peptide pepsinogen, whose role is to
break down proteins in food. After pepsi-
ngen is secreted by cells that line the stom-
ach, hydrochloric acid in the stomach mixes
with pepsinogen, converting it into pepsin
A, which digests proteins, and into several
other small fragments.

Those fragments, which previously had no
known functions, showed up as candidates in
the antimicrobial screen.

Once the researchers identified those
candidates, they tested them against bacte-
ria grown in lab dishes and found that they
could kill a variety of microbes, including
foodborne pathogens, such as Salmonella
and E. coli, as well as others, including Pseu-
donomas aeruginosum, which often infects the
lungs of cystic fibrosis patients. This effect
was seen at both acidic pH, similar to that
of the stomach, and neutral pH.

“The human stomach is attacked by many
pathogenic bacteria, so it makes sense that
we would have a host defense mechanism
to defend ourselves from such attacks,” de la
Fuente-Nunez says.

The researchers now hope to modify these
peptides, to make them more effective, so
that they could be potentially used as anti-
biotics. They are also seeking new peptides
from organisms other than humans, and they
plan to further investigate some of the other
human peptides identified by the algorithm.

“We have an atlas of all these molecules,
and the next step is to demonstrate wheth-
er each of them actually has antimicrobial
properties and whether each of them could
be developed as a new antimicrobial,” de la
Fuente-Nunez says. "

Article adapted from an MIT News Office story.
EDITCONNECT: E111806
Editor’s focus: The balance between ROI and R&D

BY JEFFREY BOULEY

IT’S ALWAYS BEEN A BALANCING ACT for pharma/biotech, and perhaps more so than ever with very high-end therapeutics like cell and gene therapies on the horizon. How do you balance the cost of the product with the cost required to bring it to market through the long and arduous process of discovery, R&D/ preclinical, clinical trials and regulatory approval?

And now there are rumblings from the White House that perhaps President Trump might consider price controls on drugs.

Now, it’s not as if the U.S. government has never considered official policies that would rein in drug costs. Particularly when it is considering the cost of running Medicare, the debate has arisen before now. And certainly, other governments that have single-payer healthcare systems tend to be aggressive in negotiating—or dictating—price points with pharma and biotech companies.

In fact, the proposed U.S. drug pricing move theoretically would use what other countries pay as a benchmark, essentially setting an interna- tional index to which the United States would hold companies with regard to Medicaid purchasing.

The concern is that such controls could dampen pharmaceutical R&D and innovation. In fact, a report released this fall by the Information Technology and Innovation Foundation (ITIF) maintains that price controls would have a negative effect on drug development by replacing biopharmaceutical indus- try investment in research, thereby slowing the pace of drug discovery.

“At the heart of the matter is the precautionary principle, which mandates that we precede innovation based on scientific evidence to ensure that safety and efficacy are maximized,” said ITIF President Rob Atkinson, author of the report. “Price controls and other steps to limit prices, such as weaker intellectual property protections, would lead to less R&D and would limit overall knowledge generation and sharing critical to new drug discovery.”

I don’t know what the chances are of this plan taking off. I don’t even pretend to know what the economic or scientific impact would be. But I do suspect that given the lack of a single-payer healthcare system in the United States, whatever burden the government offloads will be taken up by higher prices paid by everyone not covered by Medicare.

I suspect that is the more likely outcome of “price controls,” since I haven’t heard anything about the administration mandating that companies adhere to an international index for pre- scribing that is covered by private insurance or out-of-pocket payments.

In any case, rather than focusing on the end point of prices of marketed drugs, perhaps we should instead focus on how to facilitate entry into cutting-edge therapeutics so that pharma and biotech companies don’t have to take such expensive gambles by investing in therapeutic candidates that the FDA or other regulatory agencies might not even approve.

Jeffrey Bouley, DDN Chief Editor

OUT OF ORDER: BEYOND THE BUBBLE

BY RANDALL C WILLIUS

SCIENCE and medicine are about measurement. They are about the quantification of parameters that determine whether something is normal or unusual, healthy or diseased.

Throughout the scientific and medical journal world, as well as DDNews itself, we read about p-values and non-inferiority, minimal residual disease and PFS, IC50 and t½, sensitivity and specificity.

Want to convince a roomful of scientists about your new finding or approach? Show them the numbers.

Want the FDA and its compatriots to approve your therapy? Show them the numbers.

Want insurance companies or regional health plans to cover a treatment? Show them the numbers.

In science and medicine, we quest for understanding. We quest for knowledge. We quest for truth.

This is how it is, and for the past 18 years, this is how I have read, interviewed and written about science.

Something is changing, however. The nature of the quest is shifting or expanding.

Yes, we want understanding, knowledge and truth, but more and more it seems that these are no longer enough, are no longer sufficient without also including a quest for meaning.

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What science and medicine are not is health care. And healthcare cannot exist without patients and caregivers, the very people often ignored or digitized in the parameterization of health and disease.

Over the last year or so, I have noticed the shift in my conversations with pharma and biotech executives. Where once we only spoke of platforms and performance, and now we talk about people and impacts on daily lives.

For my August Special Report on Drug Delivery, I spoke with Matthias Schmidt, CEO of ArmaGen, a company developing novel enzyme replacement therapies to treat the neurological impacts of lysosomal storage diseases. And as eager as he was to talk about his company’s approach to the blood-brain barrier, Schmidt spoke of platforms and performance, and now we talk about people and impacts on daily lives.

He recounted with some emotion how game-changing the outcome of a clinical study was for some of the parents and patients.

“The parents aren’t looking for another Einstein,” he explained. “They know about the [otherwise] very serious prognosis of the disease.”

“If they can keep their kids at the stage where the disease currently is—because they know the child is going to decline—they would be the happiest people on Earth,” he continued.

“This is what we should always be reminded of. Anything that’s being done here is not for us. It’s not for the vanity of science. It’s about how we do something better to create a better world for the patients whom we serve.”

And this isn’t exclusive to my September Special Report on Stem Cells. I talked to Amander Clark of UCLAS’ Broad Center and Kyle Orwig of the University of Pittsburgh, both of whom apply stem cell technologies to improve understanding of and perhaps one day treat infertility.

Both had heartfelt recollections of the people they met in pursuing their research.

“I get emails on a weekly basis from couples who are asking me when will stem cell—IPSC particularly—technology be available so that my partner and I can have a baby,” Clark recalled. “Clearly this is a topic and a technology that is desired by members of our community.”

“If you aren’t suffering with infertility yourself, it may be hard to know what’s going on inside other people,” offered Orwig, who is also director of fertility preservation in Pittsburgh. “I can guarantee you that there is a major psychological impact on the individual and also on the couple.”

Likewise, in this month’s Special Report on Molecular Diagnostics beginning on page 20, I spoke with Kimberly Martin, vice president of reproductive health at Natera, about noninva- sive prenatal testing using cell-free fetal DNA found in maternal blood.

Yes, Martin had plenty to say about the assay technologies, detection sensitivities and fetal fractions. Anything is important to her, if not more so, however, was the human responsibility of not just providing the results to patients and partners, but also providing a sense of context, implications and limitations of the results.

“Every day, I saw the impact,” she recounts. “I tried very hard from when I was a resident until I ORDER CONTINUED ON PAGE 11

Jeffrey Bouley, DDN Chief Editor
COMMENTARY: The right way to use genetic information in clinical trials

BY JILL JOHNSTON OF WCG CLINICAL SERVICES & KARMEN TRZUPA OF INFORMEDDNA

WEN A PATIENT receives a drug or therapy, the outcomes can vary widely from good to poor, or even result in an adverse event. These outcomes may appear to occur randomly, but most variability in treatment response can be attributed to personal underlying differences. For many diseases, genetic susceptibility factors account for much of this variability.

Take the case of PARP inhibitors for breast cancer. In many patients with metastatic breast cancer, these drugs can work very well. In other patients, they may not work at all. As a result, PARP inhibitors for late-stage, triple-negative breast cancer failed to show a clear benefit. These were large, well-designed randomized studies using the traditional clinical trial model. The PARP inhibitors, in patients with BRCA-positive breast cancer, were highly successful. The difference? The early studies failed to stratify trial patients by their underlying genetic cause of disease.

As this example shows, when differences in genetic variants are accounted for in clinical trial design, interventional trials can become much more successful for particular patient groups. For example, PARP inhibitors for breast cancer failed to show a clear benefit. These were large, well-designed randomized trials using the traditional clinical trial model. The PARP inhibitors, in patients with BRCA-positive breast cancer, were highly successful.

In reality, almost every disease can be better treated through some degree of personalized medicine. Today, genetic risk factors are known for most common diseases. With personalized medicine, drugs and therapies can be targeted toward the genetic makeup of an individual rather than the disease as a whole. With targeted treatments, each of the groups may benefit.

Personalized medicine is proving to be extremely effective, but the clinical trial protocol for incorporating and utilizing this genetic data is complex. Traditional clinical trial models do not factor in the complications that arise with the incorporation of genetic testing, processes or handling of the data itself.

It’s complicated

For many physicians in clinical practice, genetic counseling can feel like a drain of time and resources. Because they may not feel comfortable ordering genetic testing or have access to genetic counselors, physicians often avoid participating in the referral process for these types of clinical trials. They may not be aware of the variety of resources available to them as they consider genetic testing for their patients. There can also be misconceptions with trial design or the anticipated process associated with the clinical trial. When investigators decide they want to participate in a study utilizing genetic testing, many assume that all they need to do is add a genetic test to their existing screening protocol. It can be much more complex than that.

The first challenge is identifying qualified patients. For trials aiming to target patients with rare diseases or rare variants associated with more common diseases, the right patients may be hard to reach. By definition, these patients are rare, and located throughout the country. They won’t be clustered near major medical centers or clinical trial sites in major areas. In addition, a huge number of patients may need to be screened during the patient identification process. For a variant that is only clinically relevant in a specific population less than 15,000 patients will need to be screened to identify 300 qualified patients.

Genetic testing for a clinical trial or natural history program is frequently completed as a pre-screening procedure, which may actually extend the screening period compared to a more traditional clinical trial. The genetic testing often takes longer to return results than a common laboratory panel. Once the results are returned, a genetic counseling session needs to be set up and if the patient tests positive for the specific variant, then additional screening processes can be completed to see if the patient actually qualifies for the specific study being investigated. Since genetic data can be unfamiliar and confusing, patients and families often have questions and need someone to explain their results. Furthermore, the patients who test negative for one trial may still qualify for another clinical trial, focusing on other genetic variants. In such a scenario, the need for genetic counselors to provide this level of support for patients and physicians all over the country, regardless of where a specific patient is actually sitting.

Education: Recently, the National Academies of Science, Engineering and Medicine recommended that clinical studies return trial results to research participants in a thoughtful and supportive manner. But providing genetic information to patients who may not know how to understand or interpret their results isn’t empowering if they aren’t also provided with the tools to use that information to make decisions about their health and their family’s health. It’s essential that genetic counseling is accessible to empower participants to make informed decisions about the results of genetic testing.

“Genetic counselors are the key ingredient to a successful use of genetic testing and stratification in clinical trials. Genetic counselors can be beneficial in many areas such as patient and provider education, engagement and retention. They can set appropriate expectations regarding the kind of information the test will provide, and they can also provide personalized education on test results. Telephone-based genetic counseling can enable sponsors to provide this level of support for patients and physicians all over the country, regardless of where a specific patient is actually sitting.”

ORDER

CONTINUED FROM PAGE 10

becoming leading physician and one into industry to meet the family where they are.

To use language that they can understand.

To try to make a bad situation as supportive as possible.”

In each interview, the weight of responsibility and the hope that they could make a difference in even a single family member were palpable. I have heard that same tone in many other conversations, as well.

There will always be an analytical dispassion to science and medicine, as much of discovery and development takes place at a distance—both physical and temporal—from its intended beneficiaries, who deal with their conditions largely invisibly. In most cases, that is as it needs to be.

But I am heartened to see a greater human connection between one end of the process and the other, because with that connection comes compassion and with compassion comes meaning. And without meaning, what is the point?"
New modeling provides a more accurate analysis of complex genetic and drug/environment data

**BY MEL J. YEATES**

**NEW YORK—** Researchers at the Icahn School of Medicine at Mount Sinai and the University of Washington designed a modeling system that integrates genomic and temporal information to infer causal relationships between genes, drugs and their environment, allowing for a more accurate prediction of their interactions over time. The work is described in a paper entitled “Temporal Genetic Association and Temporal Genetic Causality Methods for Dissecting Complex Networks,” which was published Sept. 28 in Nature Communications.

Given the complexity of biological systems, researchers believed it would only be possible to increase accuracy of prediction tools by examining gene expression and other data in response to various perturbations at multiple points over time. The tools they created measure both static and dynamic changes, in order to identify the web of causal relationships among molecular elements that make up regulatory networks.

“In general, genes X drugs/environment interactions are studied at one most informative time point, which is predefined based on some knowledge. However, most responses to drugs or environment are dynamic. It is hard to find a universal most informative time point for all possible genes X drugs/environment interactions,” mentions Dr. Jun Zhu, a professor of genetics and genomic sciences at the Icahn School of Medicine, Head of Data Sciences at Sema4 and senior author of the publication. “Instead, modeling these interactions at one specific time point, we proposed to leverage time series data and developed a temporal genetic association testing method to model genes X drugs/environment interactions.”

“Responses of gene expression traits over time are very diverse, so we used a polynomial function (of time) to describe temporal trajectories and further assumed that the temporal traits follow a multivariate normal distribution with a flexible covariance structure across subsequent time points. Then, we can test the association between the temporal traits and genetic loci with or without drugs. In addition, we developed a causality test to distinguish associations vs. causal regulations, aiming to discover molecular mechanisms of model genes X drugs/environment interactions.”

The scientists evaluated their tools by analyzing a genetically heterogeneous population of yeast cells treated with rapamycin.

**RESEARCH & DEVELOPMENT**

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**BRIEFS**

**Disease modeling, drug testing for ALS**

CAMBRIDGE, Mass.—Scientists at MIT have harnessed microfluidic chip technology to create a 3-D model of amyotrophic lateral sclerosis (ALS) on a chip that accurately models the interaction of motor neurons and muscle fibers. Neurons were generated from either healthy subjects or ALS patients. The neurons are photosensitive, enabling the engineers to control them with light, and the muscle fibers are anchored on flexible pillars so that muscle contraction can be measured by the displacement of the pillars. The team has tested two drugs with this model—rapamycin and bosutinib, both of which are in clinical trials as ALS treatments—and found the combination restored the majority of muscle pillars. The team has tested two drugs with this model—rapamycin and bosutinib, both of which are in clinical trials as ALS treatments—and found the combination restored the majority of muscle pillars. The team has tested two drugs with this model—rapamycin and bosutinib, both of which are in clinical trials as ALS treatments—and found the combination restored the majority of muscle pillars. The team has tested two drugs with this model—rapamycin and bosutinib, both of which are in clinical trials as ALS treatments—and found the combination restored the majority of muscle pillars. The team has tested two drugs with this model—rapamycin and bosutinib, both of which are in clinical trials as ALS treatments—and found the combination restored the majority of muscle pillars. The team has tested two drugs with this model—rapamycin and bosutinib, both of which are in clinical trials as ALS treatments—and found the combination restored the majority of muscle pillars. The team has tested two drugs with this model—rapamycin and bosutinib, both of which are in clinical trials as ALS treatments—and found the combination restored the majority of muscle pillars.

**Setting up for standardization**

PRESCOTT, N.C.—Weill Cornell Medicine has chosen GenExosome Technologies’ exosome isolation system to be part of the first standardization processing of cGMP-grade exosomes for clinical studies, as announced by Avahan GlobalCare Corp., of which GenExosome is a subsidiary. Dr. Yen-Michael Hsiu, director of cGMP Cellular Therapy Facility and Laboratory for Advanced Cellular Engineering at Weill Cornell, will lead a co-development program to standardize cGMP-grade exosome isolation from human endothelial cells and to identify/isolate tissue-specific exosomes for liquid biopsy and clinical use. A material transfer agreement will be established to permit Weill Cornell’s use of GenExosome’s system.

“Identification and isolation of tissue-specific exosomes is considered by many as the “Holy Grail” in this area. This co-development and standardization initiative with Weill Cornell has further enhanced the global recognition, intellectual property, as well as our leading role in this industry sector,” said Dr. Yu Zhou, founder and co-CEO of GenExosome.

**Gene, drug and environment interactions**

New modeling provides a more accurate analysis of complex genetic and drug/environment data

**BY MEL J. YEATES**

**NEW YORK—** Researchers at the Icahn School of Medicine at Mount Sinai and the University of Washington designed a model that integrates genomic and temporal information to infer causal relationships between genes, drugs and their environment, allowing for a more accurate prediction of their interactions over time. The work is described in a paper entitled “Temporal Genetic Association and Temporal Genetic Causality Methods for Dissecting Complex Networks,” which was published Sept. 28 in Nature Communications.

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The scientists evaluated their tools by analyzing a genetically heterogeneous population of yeast cells treated with rapamycin.

**Biomarkers for autism**

**QBM-001 for non-verbal children set for clinical trials in 2019**

**BY LORI LESKO**

**NEW YORK—** Targeted toward the clinical trials in 2019 is QBM-001, biotech accelerator Q BioMed’s autistic spectrum disorder candidate heads toward trials next year.

BQMB-001 is working on biomarkers and a companion diagnostic related to autism even as its autism spectrum disorder candidate...
To identify multiple genes functioning together to interact with drugs. With identified genes X drugs interactions, drug combinations can be developed to enhance or minimize the genes X drugs interactions.

Alternatively, it can be extended to study the effects of diverse perturbations on temporal traits—for example, virus-specific effects or vaccine responsiveness, as we have already implemented in another study. In addition, time scale also helps to dissect the causal relationship among different temporal traits to further illustrate the underlying molecular mechanisms and yield novel therapeutic targets.

Asked about future plans for the algorithm, Zhu says, “We are generating human temporal data in responding to experimental perturbations so that we can refine temporal genetic association and causal testing methods based on diploid system instead of haploid system in yeast. We are also extending the proposed methods to study diverse perturbations—for example, virus-specific effects among diverse strains of viruses on temporal gene expression trajectories from mouse lung or blood. This extension enables us to identify causal molecular mechanisms underlying virulent strains or genes X virus interactions so that we can develop therapies to modulate host response to a specific virus. In the future, as more data is accumulated, more complicated models will be considered to represent the comprehensive regulation relationships.”

“The temporal-genetic models enhance the power to resolve causal relationships and provide a more systematic view of the dynamic regulation mechanisms. The models can be applied to many areas, such as early cancer or other diseases detection, and precision therapeutic development,” Zhu concludes. “There are lots of directions to push.”

Zhu also adds that the model has “a great utility in precision medicine for developing drug biomarkers or drug combinations. As mentioned above, our temporal-genetic association model is not only more sensitive in identifying genes X drugs interactions than traditional single time point-based methods, which rely on predetermining time points, but is also more flexible. Traits or samples can be measured at a non-fixed series of time points. Comparing with single gene mutation-based methods (siRNA or CRISPR screening), our model has potential to identify multiple genes functioning together to interact with drugs. With identified genes X drugs interactions, drug combinations can be developed to enhance or minimize the genes X drugs interactions.”
**AUTISM**  
**CONTINUED FROM PAGE 12**

“In conjunction with the clinical trial, we have planned to validate the biomarkers, which would allow for one or both to be used as a companion diagnostic,” Derham says. “At Q BioMed, we are tackling two obstacles: a lack of genetic information and a lack of diagnostic capabilities for our subgroup ... In conjunction with the clinical trial, we have planned to validate the biomarkers, which would allow for one or both to be used as a companion diagnostic.”

Robert Derham, vice president of orphan products for Q BioMed

“Although more genetic causes are being found, not enough has been done in the past,” Derham says. “At Q BioMed, we are excited ...”

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

**RESEARCH & DEVELOPMENT**

**THEMIS**  
**CONTINUED FROM PAGE 1**

developed by the Eberhard-Karls-Universität Tübingen and the Max Planck Institute for Biochemistry, the financial terms of the agreement were not disclosed.

“We believe the longstanding expertise of Prof. Ulrich Lauer’s virotherapy research group at the University Tübingen in animal oncology, together with our measles virus product development capabilities, provides a strong foundation to rapidly develop differentiated oncolytic virotherapies,” says Erich Tauber, CEO and founder of Themis. Tauber notes that “this is the first partnership agreement between Themis Bioscience and the Max Planck-Innovation GmbH, the technology transfer organization of the Max Planck Society. Themis and the MPI group have been enjoying friendly scientific relationships over the last year, and we are now entering into a formal agreement.”

“The measles vaccine virus used by Themis Bioscience has been shown to possess inherent oncolytic capabilities, and in-vitro and animal experiments have already demonstrated the positive effects of this vector in destroying tumor cells.”

Erich Tauber, CEO of Themis

“Based on our expertise with the measles vaccine virus platform, our clinical validation and the cGMP manufacturing capabilities we developed for our infectious disease indications, we felt that accessing the IP jointly developed by Prof. Lauer’s lab at the University Tübingen and the Max Planck Institute for Biochemistry would complement our existing portfolio,” he adds. “Our focus is now to utilize the natural tumor-killing potential of the vector to treat cancer. The measles vector and its payload developed by the Lauer research group gives Themis quicker access to enter cancer indications, and we will also benefit from the expertise of Prof. Lauer to further develop virotherapies and testing them in the clinic.”

The licensed technology is a modified measles virus based on the viral genome sequence of the established measles vaccine strain, which has been used to immunize billions of people worldwide. The measles virus itself has innate anticancer properties, including mediating tumor cell lysis, T cell activation and specific tumor cell targeting. It can also be engineered to include a tumor-killing payload, making it a major building block for an effective oncolytic virus immunotherapy.

“The measles vaccine virus used by Themis Bioscience has been shown to possess inherent oncolytic capabilities (Noll et al., Int. J. Cancer 158:983, 2021), and in-vitro and animal experiments have already demonstrated the positive effects of this vector in destroying tumor cells. Of the several mechanisms involved in this process, a vital aspect concerns the ability of the measles virus vaccine virus to identify a specific receptor, CD46, on the cell surface, which is overexpressed in tumor cells and can specifically mediate its entry into cancer cells. In addition, the antitumor effect of the measles virus vaccine platform can be further enhanced by arming the vector with specific tumor killing payloads,” Tauber explains.

Our most advanced program in immuno-oncology uses an inserted diagnostic vaccine for an enzyme that catalyzes the conversion of a safe, non-toxic and licensed anti-mycoticort (5-FU, prodrug), into a cytotoxic, clinically approved, chemotherapeutic drug 5-FU. In cancer cells, 5-FU results in the inhibition of DNA and protein synthesis which triggers cell death, even in those cells resistant to virus-induced destruction (i.e., nonpermissive).” (See Figure.) “This approach allows the use of the chemotherapeutic drug in a highly targeted manner rather than a systemic applica-
tion that causes major side effects. We will further explore the potential of different tumor-killing and immune-modulatory payloads to increase the oncolytic effect or combining the oncolytic effect with other novel therapies that could enhance and possibly amplify the mechanisms of action to identify the greatest potential of the technology in cancer.”

According to Tauber, “We are currently working to target selection and optimization in immune-oncology and are considering several measles vector-based virotherapy programs equipped with tumor-killing payloads. Our goal is to bring the first program into the clinic next year. Furthermore, we will continue to expand the cancer immunotherapy potential of the platform through collaborations with external research and development partners at the forefront of oncology innovations to maximize the commercial and therapeutic potential.”

Themis has established a robust cGMP manufacturing process for its measles vector technology, and built a broad pipeline with both proprietary and partnered infectious disease vaccine candidates. The lead program in Chikungunya is anticipated to enter Phase 3 development in the near- to medium-term.

“We have seen clinical success with our platform in infectious disease, but with our lead program in Chikungunya on the verge of entering Phase 3 development, which is very exciting for us,” Tauber tells DDNews. “Based on this success, our expe-
rience, and our strategic move to expand our clinical development and management team as well as the support from our partners, we believe we have all the right ingredients to investigate the potential of our measles platform vector as novel cancer treatment in patients. The ability to accessorialize the measles vector with different tumor-killing and immune-modulatory payloads makes it a prime building block for novel immune-oncology treatments, whether alone or in combination with other novel cancer therapies with synergistic mechanisms of actions.”

“Overall this agreement is an important strategic move for us as a company we broadened our pipeline beyond infectious diseases and invest in the future growth of our company,” Tauber concludes. “These are currently very exciting times for Themis with a few key milestones upcoming, including the full results publication from our Chikungunya Phase 2 trial, [and] the initiation of our clinical development program. We are confident that our clinical team will build a strong pipeline through patent filings. The identities and experience of the CDMO and CRO will be ‘announced shortly,’ Derham tells DDNews.

“Autism spectrum disorders remain quite complex to diagnose and treat due to the varying differences or heterogeneity that abound,” Derham says. “Treating autism might be similar to Richard Nixon waging war on cancer in the early 70s and expecting to eradicate it. We know there are thousands of different types of cancers, and similarly, the number of subsets within the autism spectrum will only continue to increase. However, hopefully the autism spectrum never proves to be as segmented as cancer.”

Many parents “are frustrated that a diagnosis comes so late with autism,” Derham notes. “Parents often have that sixth sense that something is not right with their child. And with autism, unless the newborn comes from a high-risk family with a history of autism, most pediatricians or child psychologists do not feel comfortable making a diagnosis of autism until the child is at least two years of age.”

Although more genetic causes are being found, not enough has been done in the past, Derham says. But that is changing, thanks to the Simons Foundation Autism Research Initiative, which funded and started Simons Foundation Powering Autism Research for Knowledge (SPARK), a landmark autism research project in the U.S., whose mission is to speed up research and advance our understanding of autism.

“One of the biggest challenges is identifying more unique subgroups within autism,” Derham says. “As the data accumulates, so do genetic commonalities that allow researchers to identify new subgroups under the autism umbrella. Those commonalities then allow for a diagnostic to be developed.”

Not all individuals who become nonverbal will benefit from QBM-001, Derham says. However, with validated biomarkers, testing from trained specialists and genetic testing, children who fall in this targeted population can then be identified and so have a higher likelihood of responding to treatment.

“We are grateful for the feedback from clinicians, patients and their families and medical and scientific advisors,” says Denis Corin, CEO of Q BioMed. “All are excited about the roadmap for QBM-001 over the next six months and look forward to report-
ing on our progress.”

Robert Derham, vice president of orphan products for Q BioMed
This project has three main parts, and each participating university will take the lead on one segment. The first order of business is the establishment of a mathematical formula, which will be handled by Anru Zhang, a theoretical statistician and assistant professor of statistics at the University of Wisconsin–Madison. Once the formula is in hand, Ma will design algorithms that can be used to analyze data. And lastly, Chi Zhang, an assistant professor of medical and molecular genetics at the Indiana University School of Medicine, will apply the developed model—which will use single-cell RNA sequencing data—to cancer tissues.

With regards to what the South Dakota State University contingent will be responsible for, Ma says that “In this project, we propose the development of a computational infrastructure to derive gene signatures of cell-type specific TRSs from single-cell RNA-Seq data and decompose a tissue transcriptomic data to the contributions of TRSs in its component cells. Specifically, my lab will focus on the last two aims among the following three aims: (1) Mathematically model TRS and associated co-regulation gene modules through transcriptomic profiles of single cells; (2) Develop a novel bi-clustering algorithm for identifying condition/cell-type specific co-regulated gene modules in single-cell transcriptomic data; and (3) Identify and annotate the gene signatures for each TRS, and estimate the level of each TRS in independent tissue data. All the developed computational tools and derived knowledge will be maintained into a web server/database for public utilization.”

Given that there are 20,000 genes in the human genome, and each cell’s expression of its genes affect the cell’s function, there’s a lot of information to unlock in this work—particularly since gene expression can also change due to disease.

“A gene’s expression in an individual cell is regulated by a set of transcriptional regulatory signals (TRSs) such as transcription factors, miRNAs, IncRNA and epigenomic regulators,” Ma explains. “Deciphering cell-type specific expression contribution is equivalent to identifying the true cell-type specific TRSs in different cell components of a tissue sample. Recent studies revealed the crucial impact of stromal and immune cells on the progression and metastasis of cancer. We will apply the computational methods to TCGA tissue expression and single-cell expression data from other sources, to quantitatively estimate the level of cell-type-specific TRSs for different cell types within a cancer tissue.”

“Considering that the highly diverse TRS types in mammalian cells cannot be simultaneously measured by current experimental methods, we will model and quantify cell-type specific TRSs via mathematically well-defined co-regulation modules of their regulated genes based on single-cell RNA-Seq data,” he continues. “We hypothesize that the genes co-regulated by a common TRS in multiple cells can be characterized in single-cell RNA-Seq data and form gene signatures of the TRS. Mathematically, such a problem can be formulated as detection of a submatrix in a single-cell expression matrix, where the genes share coherent expression patterns over certain single-cell samples.”

The models in this project will be developed using stromal and immune cells, according to Ma. He tells DDNews that this approach could have potential in other diseases outside of cancer, noting that “The proposed computational techniques can be robustly applied to other diseases besides cancer where heterogeneous cell types exist in the tissue.”

“Most biological techniques collect 1,000 cells in a tissue and assume the way in which the genes are expressed is identical—that is not the case,” says Qin Ma of South Dakota State University. “Each tissue contains multiple cell types and each has its own regulatory mechanism.”

ARE YOU PIPETTING SAMPLES BETWEEN DIFFERENT LABWARE FORMATS?

Motorized tip spacing enables parallel transfers of multiple samples between labware of different sizes and formats. The tip spacing can be changed by the simple push of a button, no manual adjustments or two handed operations are needed.
And the sheep shall lead them...

Day-blind sheep bring potential relief for human eye conditions into focus

BY KRISTEN SMITH

JERUSALEM—It started with a call from a concerned Israeli farmer. Beginning in 2003, the shepherd had noticed some sheep in his flock displaying signs of day blindness. Over the next five years, the prevalence in the herd grew—until he finally reached out to Dr. Ron Ofri, an associate professor of veterinary ophthalmology at Hebrew University of Jerusalem. Upon examination, Ofri determined the sheep all suffered from CNGA3 achromatopsia, a genetic mutation causing affected animals to experience blindness during the day and limited vision at night.

Together with scientists from the Hadassah Medical Center and the Agricultural Research Organization/Volcani Center, Ofri found that the sheep's condition was the result of an identical genetic mutation to one gene that causes the same condition in humans.

Dr. Ron Ofri at the Hebrew University of Jerusalem and colleagues found success in treating day blindness in sheep with gene therapy, and now two of the world's most important pharma regulatory bodies have granted orphan drug designation to the experimental therapy for human trials.

Possible FOP therapy shines in preclinical study

BLU-782 offers hope for patients with difficult-to-target genetic disease that turns muscle to bone

BY JIM CIRIGLIANO

CAMBRIDGE, Mass.—Blueprint Medicines presented promising preclinical proof-of-concept data for its investigational therapy designed to target mutant activin-like kinase 2 (ALK2)—the underlying cause of fibrodysplasia ossificans progressiva (FOP)—at the 2018 American Society for Bone and Mineral Research (ASBMR) Annual Meeting in Quebec, Canada, on Sept. 30. The investigational compound, BLU-782, showed in preclinical studies in a genetically accurate FOP model to prevent injury- and surgery-induced heterotopic ossification, reduce edema and restore healthy tissue response to muscle injury.

Blueprint Medicines, which specializes in the development of targeted kinase medicines for patients with genomically defined diseases, is developing BLU-782 as an oral precision therapy for FOP. The results indicate potent antitumor efficacy of Apogenix’s HERA-CD40L, which acts directly on cells of the innate immune system as well as on antigen-presenting cells, thereby promoting specific T cell-mediated antitumor immunity.

As the company notes, HERA-CD40L—in contrast to antibodies—does not depend on Fcγ receptor-mediated crosslinking for activity, adding, “As the first pure CD40 receptor agonist with a well-defined mechanism of action, HERA-CD40L is not restrained by dose-limiting toxicities observed with anti-CD40 antibodies.”

According to Apogenix, the strong antitumor efficacy of HERA-CD40L was demonstrated in multiple in-vitro and in-vivo tumor models. In the case of the former, comprehensive in-vitro analysis of the mechanism of action revealed that HERA-CD40L induced the development of pro-inflammatory antigen-presenting cells, including B cells, macrophages and T cells.

Of antigens and antitumor effects

Preclinical efficacy data of Apogenix’s HERA-CD40L was published in Journal of Immunotherapy

BY JEFFREY BOULEY

HEIDELBERG, Germany—Apogenix, a biopharmaceutical company developing next-generation immuno-oncology therapies, has had a pair of publications recently highlighting progress for its oncology therapeutics, most recently with the Oct. 11 news that data had been published in the Journal of Immunotherapy. The results indicate potent antitumor efficacy of Apogenix’s HERA-CD40L, which acts directly on cells of the innate immune system as well as on antigen-presenting cells, thereby promoting specific T cell-mediated antitumor immunity.

While the FOP gene was discovered more than a decade ago, efforts to develop a selective ALK2 inhibitor faltered due to technical challenges,” says Dr. Marion Dorsch, Blueprint Medicines’s chief scientific officer. “Specifically, it proved difficult to technical challenges, “ says Dr. Marion Dorsch, Blueprint Medicines’s chief scientific officer.
humans. And, in another recent discovery, a veterinary clinician specializing in ovine retinal conditions uncovered a novel therapy that might see approval one day soon to treat day blindness in humans.

According to Ofri, “Achromatopsia (ACHM) is an inherited retinal disorder that specifically prevents cone photoreceptors from functioning. ACHM is characterized by severely reduced visual acuity of 20/200 or worse, disabling light sensitivity (photophobia) and involuntary back-and-forth eye movements (nystagmus).” ACHM occurs in approximately one in 30,000 people in the United States, with 92 percent of cases caused by mutations in CNGB3 and CNGA3 genes. The condition severely limits a person’s sight by preventing cone photoreceptors in the eye from functioning, leaving most affected individuals legally blind from birth.

Ofri and his team were completely surprised to find a large animal model of a mutation occurring in people, and decided to try gene therapy on the sheep. They injected a virus carrying a mutated copy of the gene beneath the retina of nine of the affected sheep, which began producing the missing protein and restoring day sight in the flock. According to a recent article published in Human Gene Therapy journal, now six years beyond the original treatment, results show significant, long-term improvement in cone function, demonstrating a robust rescue effect following a single treatment with a viral vector that provides episomal delivery of the transgene. In other words, the sheep experienced immediate recovery of cone photoreceptor function after a single injection, and can still see today.

“Confirmation of the concept of ‘once-in-a-lifetime’ gene therapy for genetic blindness depends on patient, careful studies such as these,” says the journal’s editor-in-chief Dr. Terence R. Flotte, who is also the Celia and Isaac Haidak Professor of Medical Education, and dean, provost and executive deputy chancellor of the University of Massachusetts Medical School. “Human gene therapy investigators in the field of retinal diseases should find these results very encouraging as they move forward in expanding clinical applications of the platform of rAAV gene therapy.”

And indeed, human researchers and regulators do find the results encouraging. Both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency’s Committee for Orphan Medicinal Products have awarded orphan drug designation to AAV-CNGA3, leading private companies such as MeiraGTx Holdings to embark on human clinical trials. In addition to AAV-CNGA3, MeiraGTx also has orphan designation in both the United States and European Union for three other inherited retinal disease gene therapy product candidates: AAV-CNGB3, AAV-RPGR and AAV-RPE65, all of which are in clinical development.

“Without any currently approved therapies [for achromatopsia], we are very pleased by the FDA’s decision and the recognition from the agency that those suffering from ACHM are in need of urgent treatment options,” said Dr. Alexandra Forbes, president and CEO of MeiraGTx. “This designation is the second important regulatory milestone we’ve received for AAV-CNGA3 in just two months, and we look forward to continuing the momentum in this program for those in need of relief from this debilitating disease.”

For Ofri, the human breakthrough initiated in his veterinary practice is thrilling. “It has been an amazing adventure to take a clinical case of a disease in sheep, and be able to run with it. To be a part of possibly alleviating day blindness in people is something I never thought, as a veterinarian, I would do. It is a great sense of satisfaction for me.”
Moleculin announces new data discovery for presentation at Society for Neuro-Oncology meeting

BY DDNEWS STAFF

HOUSTON—Moleculin Biotech Inc., a clinical-stage pharmaceutical company focused on the development of oncology drug candidates, all of which are based on license agreements with The University of Texas System on behalf of the M.D. Anderson Cancer Center, announced recently that new data relating to its molecule WP1122 would be presented at the Society for Neuro-Oncology Annual Scientific Meeting to be held Nov. 15-18 in New Orleans.

“We continue to make progress in the development of glycolysis inhibitors,” said Dr. Donald Picker, Moleculin’s chief scientific officer. “We believe that we have discovered new data during our IND-enabling research with animals that confirms a highly beneficial metabolism of WP1122 and significant organ accumulation of the inhibitor of glycolysis in the brain and also in the pancreas.”

Dr. Donald Picker, chief science officer of Moleculin

“With this approach, we aim to rapidly and with structure-based medicinal chemistry, our rare disease focus area, “she remarks. The company is also engaged in preclinical development of additional drug candidates, including additional STAT3 inhibitors and compounds targeting the metabolism of tumors.

Blueprint Medicines credits the success in finding a potential cure to fibrodyplasia ossificans progressive—one that seems to lack critical off-target ill effects—to its proprietary compound library, which, according to the company’s chief scientific officer, “has been fully annotated against the human kinome.”

“BLU-782 is a cornerstone program within our rare disease focus area,” she remarks. “Importantly, BLU-782 also highlights the power of our scientific platform, and our unique ability to design highly selective therapeutic candidates for difficult-to-drug disease targets.”

“FOP is a devastating rare genetic disease caused by mutations in the ACVR1 gene, which encodes the protein kinase ALK2. Mutant ALK2s cause damaged soft tissue—such as skeletal muscle, ligaments and tendons—to regrow as bone. Beginning in childhood, disease manifestations include painful flare-ups in the form of swellings, abnormal bone formation and locking of joints, progressive loss of mobility, and respiratory dysfunction. Premature death typically occurs in middle age due to cardiopulmonary complications. There are no approved therapies for FOP, and the current standard of care—typically corticosteroids and pain medications—generally focuses on the alleviation of symptoms associated with disease flare-ups. “We currently estimate a prevalence of about 1,100 patients in major geographies, including the United States, EU5 countries and Japan,” notes Dorsch. “In addition, we continue to evaluate emerging data characterizing FOP epidemiology. For example, recently published independent data from a French registry estimated a prevalence of 1.36 per million inhabitants.” (Baujat, et al. Orphanet Journal of Rare Diseases, 2017.)

Blueprint Medicines owns worldwide development and commercialization rights for BLU-782. The company plans to submit an Investigational New Drug application for the compound to the U.S. Food and Drug Administration by the end of 2018. If approved, Blueprint Medicines is prepared to proceed with a Phase 1 trial.

“We plan to initiate a Phase 1 clinical trial of BLU-782 in healthy volunteers in the first quarter of 2019,” says Dorsch. “Our goal is to advance BLU-782 into a Phase 2 clinical trial in patients with FOP, though we have not yet guided to when this trial may be initiated.”

Ablexis inks licensing deal with Memorial Sloan Kettering

Agreement grants rights to research, develop and commercialize antibodies generated using AlivaMab Mouse platform

BY DDNEWS STAFF

SAN DIEGO—Ablexis LLC, a biopharmaceutical company focused on its AlivaMab Mouse technology for antibody drug discovery, has announced a license agreement with Memorial Sloan Kettering Cancer Center. The license grants Memorial Sloan Kettering rights to research, develop and commercialize—with rights to sub-license—certain AlivaMab antibodies against a specific target.

The antibodies were generated by the Tri-Institutional Therapeutics Discovery Institute Inc. under a non-exclusive license of AlivaMab Mouse announced in January 2017. Under this new license, Ablexis could receive clinical development and approval milestones, and a running revenue share of sales of products derived from the AlivaMab antibodies.

“The AlivaMab Mouse is an increasingly validated platform for generating antibodies with qualities desirable in a potential therapeutic,” said Dr. Larry Green, CEO of Ablexis. “This agreement with Memorial Sloan Kettering exemplifies the speed and value-add that the AlivaMab Mouse can bring to a therapeutic antibody discovery program.”

The AlivaMab Mouse is designed to enable and optimize the efficient discovery and development of the next generation of human therapeutic antibodies. The platform has been validated for antibody drug discovery by Ablexis and partners in various formats—including regular antibodies, bispecifics and chimeric antigen receptor T cell therapies—and for a range of applications, such as:

• Sequence diverse panels of monoclonal antibodies (mAbs)
• Epitope diverse panels of mAbs
• Challenging targets such as G-protein-coupled receptors
• Challenging design goals such as IC50 values of very low picomolar levels.

Ablexis has non-exclusively licensed the AlivaMab Mouse technology to multiple companies, including global pharmaceutical companies, public and private biotechnology companies and other entities.

BLU-782 continued from page 16

to selectively target ALK2 without inhibiting other members of the ALK family, including ALK1, ALK3 and ALK6, which have the potential to drive off-target toxicity.”

In the preclinical studies, BLU-782 demonstrated exquisite selectivity for R206H mutant ALK2 in cellular assays while, importantly, sparing closely related anti-targets ALK1, ALK3 and ALK6. Additionally, BLU-782 potently inhibited mutant ALK2 in vitro, regardless of the activating ligand, including activin A, activin B and BMP6. In vivo studies in a conditional knock-in ALK2R206H transgenic mouse model showed BLU-782 prevented the formation of injury-induced heterotopic ossification and edema, restored a healthy response to tissue injury—including skeletal myofiber regeneration—and prevented the formation of surgery-induced heterotopic ossification following fibular osteotomy surgery.

The company sees the promising preclinical results as a credit to its scientific platform, including the proprietary compound library that serves as its centerpiece, from which BLU-782 was derived.

“The library includes novel chemical matter developed by Blueprint Medicines that has been fully annotated against the human kinome,” says Dorsch. “With the library, we are able to take a kinase disease target—such as ALK2—and identify selective starting points. With these starting points, we then optimize drug candidates with structure-based medicinal chemistry. With this approach, we aim to rapidly and reproducibly develop highly selective drug candidates. BLU-782 is the embodiment of our approach.”

According to Dorsch, Blueprint Medicines’ portfolio strategy focuses on using their scientific platform to develop targeted and potent kinase medicines in three areas: genonomically defined cancers, rare diseases and cancer immunotherapy.

“BLU-782 is a cornerstone program within
immune response and evaluate the critical role in the antitumor superfamily receptors that play technology to address other TNF.

As explained in the company news release about the published data, “The potent antigen-specific activation of T cells by HERA-CD40L-treated macrophages led to an immune response specifically directed against the tumor. This is an important advantage over numerous other immunotherapeutic approaches that often cause serious side effects due to non-specific activation of the immune system.”

The company maintains that HERA-CD40L “is perfectly suitable for standard large-scale production processes,” and says that its mechanism of action as a central mediator of T cell activation and co-stimulation “predestines” this molecule for combination therapies, such as adding it along with radiotherapy or checkpoint inhibitors.

“HERA-CD40L is a novel TNF [tumor necrosis factor] superfamily receptor agonist based on our proprietary HERA-ligand technology platform that has demonstrated a strong antitumor efficacy in preclinical tumor models,” said Dr. Harald Fricke, chief medical officer of Apogenix. “HERA-CD40L is a novel TNF superfamily receptor agonist based on our proprietary HERA-ligand technology platform that has demonstrated a strong antitumor efficacy in preclinical tumor models.”

As with HERA-CD40L, Apogenix touts the distinction of HERA-CD27L compared to antibodies against cancer that are currently in clinical development. In the Frontiers of Oncology paper, data indicate that HERA-CD27L treatment boosted specific T cell activity while having no effect on regulatory T cell activity or survival, which Apogenix says “is a great advantage over other strategies in development, which have been shown to lead to serious immune-related adverse events due to their ill-defined mechanisms of action.”

The company has built what it calls “a promising pipeline” of immuno-oncology drug candidates that target TNF superfamily-dependent signaling pathways, thereby restoring the immune response against tumors. Checkpoint inhibitor asunercept, the company’s lead immuno-oncology candidate, is in late-stage clinical development. In 2017, asunercept received PRIME (PRIority MEdicines) designation by the European Medicines Agency for the treatment of glioblastoma.

The company noted that HERA-CD40L has shown significantly enhanced activity compared to a clinical benchmark anti-CD27 antibody and that combining HERA-CD40L with an anti-PD-1 antibody revealed additive antitumor effects, highlighting the importance of both T cell co-stimulation and checkpoint inhibition in antitumor immunity.

Apogenix has developed a proprietary technology platform for the construction of novel hexavalent TNF superfamily receptor agonists (HERA-ligands). By stimulating different TNF signaling pathways, these HERA-ligands can increase the antitumor immune response. The specific molecular structure of Apogenix’s HERA-ligands induces a well-defined clustering of functional TNF receptors on the surface of target immune cells. In contrast to agonistic antibodies, Apogenix’s fusion proteins are pure agonists whose potent signaling capacity is independent of secondary Fc receptor-mediated cross-linking. In addition, HERA-ligands reportedly cause neither antibody-dependent cellular cytotoxicity nor complement-dependent cytotoxicity and exhibit a shorter half-life than antibodies. It is therefore expected that HERA-ligands will cause fewer side effects in clinical development.

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Cancer characterization leads to fetal monitoring

BY RANDALL C WILLIS

The woman lies on the table, her partner at her side, holding her hand as the physician slides the ultrasound probe across her skin, eyes glued to the monitor. It’s obvious that the growth has changed since the last test. It’s gotten bigger. The tissues have changed. And where this might be bad news for someone with a diagnosis of cancer, the news is brighter for the expectant mother and her burgeoning family.

Although the comparison of a developing fetus to a cancerous tumor may seem callous, there are a lot of biological and technological parallels between the two.

According to Kim Martin, vice president of global women’s health at Natera, one of the first people to openly describe the parallels between the placenta and a tumor was Dennis Lo of the Chinese University of Hong Kong (CUHK).

“I thought a baby living in a mother is a little bit like cancer growing in a patient,” he said in a 2013 interview with The Guardian. “So, if cell-free tumor DNA can exist in a patient’s blood, surely there can be some cell-free fetal DNA in a pregnant mother’s blood.” It was this thinking that led Lo to develop what is now described as noninvasive prenatal testing (NIPT) or screening (NIPS). Within days, he recounted, he had developed a technique for treating a pregnant woman’s plasma and used polymerase chain reaction testing, or PCR, to look for evidence of the Y chromosome. The experiment, later published in The Lancet, was a success. And yet, it took a while, he emphasized, for the community to see beyond the initial findings. “They didn’t realize how far this technology could go,” Lo said. “They thought you could use it only to tell the sex of the baby.”

Part of the impetus for NIPT was the problem that traditional fetal diagnostic methods—amniocentesis and chorionic villus sampling (CVS)—came with risks, including a 1 percent or so spontaneous miscarriage rate. A safer way to perform at least a preliminary screen was needed (see sidebar article, “Detecting anomalies,” on page 25).

Working with Sequenom (now part of Integrated Genetics), Lo launched the first commercial NIPT for Down’s syndrome (trisomy 21) in 2011, and more recently, tests for Edwards (trisomy 18) and Patau (trisomy 13) syndromes. And...
until recently, broad chromosomal anomalies were the sole domain of NIPT.
But with cell-free DNA (cfDNA) itself, technological innovations continue to push those boundaries.

HOMING IN
In a recent editorial, Lyn Chitty of Great Ormond Street Hospital for Children suggested that most of the literature on NIPT has focused on chromosomal anomalies, screening for aneuploidy, which has resulted in “a significant reduction in invasive testing and consideration for first-line Down syndrome screening.”

“Far less attention has been given to noninvasive prenatal diagnosis (NIPD) for monogenic disorders,” she continued, “as there is virtually no commercial interest and development is costly and largely done on a bespoke family-by-family basis.”

This imbalance is shifting, however, according to Martin, as cfDNA screening increasingly probes ever-shrinking targets from microdeletions to single-gene disorders where the change might be a single nucleotide. Her company, for one, is pushing that evolution.

“Natera really launched microdeletion pretty early on, shortly after they launched their five-chromosome test: 13, 18, 21, X and Y,” she explains, adding that the most important microdeletion is probably 22q11.2.

“It is the most common, with an incidence somewhere between one in 1,000 prenatally to one in 4,000 to 6,000 post-natally, across maternal age.”

And knowing the mutation is there opens the door to early intervention into the disorders triggered by the genetic change.

“Early intervention for the cardiac defects, many of which may not be detectable by ultrasound and may have significant morbidity if unrecognized,” she elaborates, “as well as early intervention for developmental disability or intellectual differences.”

As an example, she offers hypocalcemia as a common pathology of 22q.

“There’s clear evidence that early recognition and treatment of low calcium levels made a difference in the intellectual functioning as adults, suggesting effects of hypocalcemia on early brain development,” Martin continues. “We don’t routinely measure calcium in all infants, but a kid who’s at risk for 22q sure needs their calcium evaluated and replaced if they’re hypocalcemic.”

As the targets get smaller, however, the need for a greater number of target molecules becomes more important. This is where issues of fetal fraction—the amount of fetal cfDNA vs. the maternal background—becomes a bigger issue.

“As the fetal fraction is lower, it is kind of a question of how many needles did you put in the haystack,” Martin explains. “The more needles there are, the easier it is to find one. And that is especially true when the needles get really small. A microdeletion is like a very small needle.”

For this reason, the company cannot simply quantify all of the fragments from chromosome 22 and calculate a z-score. Instead, they amplify and sequence more than 2,000 SNPs from the critical region of 22q, giving them a higher sensitivity for the small missing pieces.

“The number of times a specific fragment is amplified, our depth of read, is higher per region than shotgun approaches,” she continues. “We take 14,000 SNPs, but we only divide them between five chromosomes. We take 2,000 SNPs, but we only have them for the critical region of 22q.”

Last year, University of Connecticut Health Center’s Peter Benn.

PRENATAL CONTINUED ON PAGE 22

Covering the News of Pharma, Biotech & Life Science

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and colleagues at Natera, including Martin, examined a revised microdeletion detection protocol that included not only 22q11.2, but also four other microdeletions associated with disorders like cri-du-chat and Angelman syndromes. The new method allowed the researchers to reduce the false-positive rate (FPR) from 0.33 percent to 0.07 percent and increase positive predictive value (PPV) to 44.2 and 31.7 percent for 22q11.2 and the other microdeletions, respectively.

“Prior publications have questioned the use of NIPT as a screening test for microdeletions, citing concerns about high FPRs, low sensitivities, and challenges associated with variants of unknown significance,” the authors wrote. “However, these reports focused on whole-genome sequencing (WGS) approaches that employ counting-based methodologies.”

“By concentrating on specific genomic regions with clinically significant deletions, the targeted nature of the SNP-based method overcomes many of the limitations discussed in these publications,” they continued. “Furthermore, comparison of detection rates for confirmed microdeletions in clinical cohorts and ratios of maternally inherited vs. de-novo deletions to published ratios suggests that SNP-based methods have substantially higher sensitivity than counting-based methods.”

They suggested that their findings supported the idea of offering microdeletion screening as “an adjunct to existing NIPT for the five clinically significant, well-characterized genetic disorders,” something they argued was consistent with American College of Medical Genetics and Genomics (ACMG) guidelines.

Natera is not alone in pursuit of 22q11.2 microdeletions in cfDNA. Last year, Maximillian Schmid and colleagues at Ariosa Diagnostics (part of Roche) and Université Libre de Bruxelles published their efforts to detect microdeletions using a number of microarray platforms focused on a ~3Mb region of 22q11.2. The researchers screened more than 1700 maternal plasma samples. In 122 samples with deletions ranging from 1.96-3.45 Mb, analytical sensitivity was 75.4 percent, while specificity in the remaining presumed unaffected samples was at least 99.5 percent. Clinical validation with samples of known microdeletion status offered similar results.

The next challenge for researchers was then to go from finding short missing fragments to identifying mutations at the single-gene level, which for Natera’s Vistara platform, means 30 specific genes. As Martin explains, to be selectable, those 30 genes needed to meet certain criteria.

“We picked things that were relatively common,” she says, suggesting one in 10,000 as a standard frequency. “We picked genes that were amenable to sequencing with a high sensitivity,” she adds. “And also disorders that tend not to present with ultrasound findings. These are things where if the ultrasound findings are there at all, they are often not there until after 24 weeks and they are often very nonspecific.”

Another criterion, she explains, was that the diseases caused by the mutations were serious.

“I don’t like the term severe,” Martin offers. “I think severe means different things to different people.”

Rather, she sees serious conditions as those that are going to require medical attention—conditions requiring more pediatric visits than the standard vaccination schedule and medical or surgical interventions. And perhaps most importantly, the company looked for mutations that were de novo, where the parents remained unaffected.

“They’re in regions that are prone to new mutations,” Martin notes. “That’s why 22q is the most common microdeletion; it’s a region with a high number of repeat sequences that are prone to mismatch during mitosis.”

At the same time, mutations might occur elsewhere in the genome of developing fetuses, and so there has been increasing interest in applying other next-generation sequencing techniques to piece together a more complete image of fetal health.

In a recent review, Chitty and colleagues discussed the promises, pitfalls and practicalities of prenatal whole-exome sequencing (WES). “The concept of prenatal screening has evolved from search and destroy to search, educate and optimize. What does optimize mean? It’s going to mean different things to different families, but it sure means a lot more than interruption of pregnancy,” says Kim Martin, vice president of global women’s health at Natera. “Many families continue affected pregnancies, and the key is that they work with their health providers to develop the absolute best care plan for that infant, whatever that means for that family ... There is no question that the technology has expanded to a point that is beyond the ability of either a provider or patient to make informed decisions about what we should be doing.”

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Molecular Diagnostics

The umbrella term “molecular diagnostics” encompasses a wide variety of techniques and technologies that are employed to analyze biological markers in an individual’s genome and proteome—that is, respectively, the genetic code and how cells express their genes in the form of proteins. Thus, molecular diagnostics brings together the 20th-century development of molecular biology with the more longstanding field of general medical testing to diagnose and monitor disease, detect risk and decide which therapies might work best for individual patients. Of course, given the genomic component, molecular diagnostics is also considered a key part of eventually realizing the dream of true personalized precision medicine.

Molecular biology itself has its original roots in the 1950s, but found its greatest growth (and clinical applications) in the late 20th century. In fact, in keeping with the prenatal focus of this molecular diagnostics special report, it is worth noting that a key piece in the maturation of molecular biology was work in 1970 by Yuval Wizak and colleagues at Aarhus University Hospital’s IDA Vogel in the launch announcement: “It is truly groundbreaking that cell-based testing may be able to identify not only chromosomal aneuploidies, but also smaller aberrations, such as microduplication and translocation, that currently can only be viewed through CVS and other invasive procedures.”

PRENATAL CONTINUED ON PAGE 24

INTO THE WEEDS: cfDNA screening increasingly probes ever-shrinking targets from microdeletions to single-gene disorders where the change might be a single nucleotide.
MEETING CRITERIA: The 30 mutations screened in Natera’s Vistara needed to match four parameters: high frequency; effectively invisible to ultrasound; trigger serious medical conditions; and not inherited (de novo).

PRENATAL

CONTINUED FROM PAGE 23

In fact, it was in these smaller perturbations where Singh and colleagues noted the advantage of cell-based methods.

“Currently, the NIPT field has largely been dominated by methods targeting cell-free fetal DNA in the maternal blood,” they wrote. “Even though these methods can reliably detect incidence of common aneuploidies (T21, T13 and T18), they have been ineffective in detecting CNVs, which constitute another major chunk of prenatal abnormalities.”

“This is mainly due to the fact that fetal DNA circulating in maternal blood is fragmented and is mixed with maternal DNA,” they explained. “Intact fetal cells circulating in maternal blood can mitigate this shortcoming of the cell-free NIPT, because they are the sources of pure fetal genomes.”

Another advantage of cell-based vs. cfDNA approaches, according to Rivelli, is timing.

“Typically, those cells show up in the mother’s blood stream earlier in pregnancy,” he elaborates. “Researchers are finding them as early as seven weeks of gestational age. So there may be some circumstances where the earlier you can get information, the better.”

Even if Singh’s platform criteria are achieved, however, cell-based NIPT efforts are challenged by another parallel from the oncology world: cellular heterogeneity.

Where a tumor is comprised of a number of cells occupying different and constantly evolving mutational states, gestation is comprised not just of the fetus but also of the placenta—and these two components do not necessarily experience mutation in the same way, resulting in fetoplacental mosaicism. “We know pretty clearly the rate of mosaicism for whole chromosome abnormalities because of CVS,” says Natera’s Martin. “For microdeletions, there are reports now for confined placental mosaicism for 22q.”

“So, we don’t know how often a microdeletion is present in the actual fetus, but we know that when you start looking at these rare things or these things like trisomy 16 or trisomy 22, they are much more likely to be confined to the placenta and not in the fetus,” she adds.

One way to compensate for any potential mosaicism is to look specifically for cells from both the fetus and the placenta, as was published last year by Changhua Christian Hospital’s Ming Chen and colleagues. In their proof-of-concept study, the researchers designed a microfluidic platform they called Cell Reveal, to which they attached anti-CD71 antibodies to capture extravillous cytotrophoblasts (EVT). They then verified the fetal and placental origins of the cells using FISH, whole-genome amplification (WGA) and short tandem repeat (STR) analysis.

Using the microchips, the researchers were able to collect 1-44 nRBC/2 mL and 1-32 EVT/2 mL maternal blood. Likewise, molecular analysis of the harvested cells revealed correct diagnoses of respective chromosomal trisomy in each sample.

“To the best of our knowledge, this report is one of the very few studies on the successful use of circulating fetal cells for noninvasive prenatal diagnostic,” the authors concluded. “The strength of our study is that all the processes of cell capture are automatic which can be performed on a single individual case and completed within 15 h. The captured cells are available for a variety of genetic testing, such as FISH, aCGH and NGS.”

For its part, although the Savran platform currently only looks at trophoblasts, Rivelli is less concerned about the mosaicism issue if only because of how the company designed its system.

“We have the ability to capture and sequence single cells,” he explains. “Let’s say we have a patient sample and find eight trophoblasts; he continues. “We’re able to capture each one, one by one by one, and sequence them individually. That helps us tease out mosaicism if that turns out to be a problem.”

“Single-cell sequencing is really developing, and single-cell RNA techniques are really coming along, so things you couldn’t do even five years ago are now pretty easy.”

Savran’s platform is still a work in progress, however.

“The workflow is such that it requires a little bit more attention and some manual steps,” Rivelli notes. “We think that to
One part of the challenge is that as with so many other biomedical efforts, including cancer, we’ve quickly moved from academic questions of what we can do to more philosophical questions of what should we do. “There is no question that the technology has expanded to a point that is beyond the ability of either a provider or patient to make informed decisions about what we should be doing,” Martin says.

What is the goal of this, she asks? How much information should people have, do people want? What do we do when we find variants that we don’t know the significance of? What are the ethics of offering that information to a pregnant family?

“We are at a crossroads,” Martin presses. “Questions are being asked that were never asked in the ‘80s or the ‘90s.”

“Nobody asked should we really be screening for Down syndrome. It was taken for granted that because we could, we should.”

And yet, she continues, one of the complaints about cfDNA and sources of resistance to making it available to all women is: What if we find something we don’t know the significance of?

“Why didn’t we ask the questions then, and why are we suddenly saying that now it’s not a good idea?” Martin asks. “It’s okay for 35-year-olds, but it’s not okay for 28-year-olds.”

Rivelli then layers on the possibilities of intervention, linking recent developments with technologies such as CRISPR.

“[Recently], there was a successful gene-editing of a mouse fetus using CRISPR technology,” he recalls. “You’re getting to the point where not only are you able to diagnose something in the fetus, you might also be able to intervene. But then you really get into an interesting conversation.”

For Martin, though, it goes back to the individuals receiving the NIFT results.

“Ultimately, the family should decide what information they want,” she asserts. “And it’s our job as medical professionals to be able to give them the tools they need to make those kinds of decisions. Those are the basic principles that I support as an OB geneticist.”

TROUBLESHOOTING

Detecting anomalies

Is my baby healthy?

It’s a primary question for every parent, one that may be asked with some trepidation.

“We know that 3 to 5 percent of babies are born with some birth defect or handicapping condition,” offers Kimberly Martin, vice president of global women’s health at Natera and formerly a practicing obstetrician and gynecologist. “And there are all different types of abnormalities.”

“There are chromosome abnormalities like Down syndrome,” she lists off. “There are single-gene disorders like cystic fibrosis or osteogenesis imperfecta.”

Between those extremes, she adds, there are microdeletions and duplications.

But the biggest group of anomalies, according to Martin, are birth defects such as cleft lip, heart defect or club foot.

“When karyotyping came on the scene in the ‘40s and ‘50s, it suddenly became possible to offer testing,” she says, and so by the ‘60s, the primary question was how old the mother will be when the baby’s born. If you said you were 35, you were high-risk, and you were offered testing,” she explains. “If you were less than 35, you were told you were low-risk, and you had a baby.”

By the late ‘80s, maternal hormone measurements were added to the repertoire, including α-fetoprotein, which is part of the quad or quadruple screen. And a decade later, ultrasound features became another screening tool, all designed to give families a greater sense of the risk level for the fetus.

“The thing with many screening tests is that it’s not a yes or no,” Martin cautions. “If I ask how old you are at delivery, and you say 35, that doesn’t mean you’re going to have a baby with Down syndrome. But you’re at higher risk and you get offered invasive testing.”

Likewise, she continues, serum screens identify about 5 percent of pregnancies as being high risk, and yet when given more invasive tests such as amniocentesis or chorionic villus sampling, more than 95 percent of those women were told their babies were fine.

The identification of fetal cfDNA in maternal blood changed the landscape.

“Doctors who had for years been scarred by the 3 to 5 percent of pregnant women with a positive predictive value of 3 to 4 percent, suddenly said well, gee, how does cfDNA perform?” Martin recounts.

“We found out that it has a sensitivity of about 98 percent or greater for Down syndrome,” she says. “It has a false-positive rate of less than 0.5 percent. It has a positive predictive value of about 90 percent.”

For a screening test, she concludes, it seems like a big win.

The win, however, is tempered by a caution: “Questions are being asked that were never asked before,” she says. “‘What is the goal of this?’ ‘What if we find something we don’t know the significance of?’ ‘What are the ethics of offering that information to a pregnant family?’

For Martin, it must always come back to the families.

“Every day, I saw the impact,” she recalls. “I talked to families who had a high-risk screening test. I talked to families who had a definitive abnormality on ultrasound. I talked to families who had an abnormal amniocentesis.”

“I tried very hard from when I was a resident until I became an attending physician and on into industry to meet the families where they are,” she continues. “To use language that they can understand. To be available and approachable to be asked questions. To try to make a bad situation as supportive as possible.”

Although progress has maybe been slower than she expected, Martin says she knew cfDNA was going to revolutionize how we approached prenatal screening.

“I don’t think it’s going to be too much longer before women are going to have that choice as a first-line choice, and not have to go through all the hoops to get that test,” she enthuses. “And I hope it happens sooner rather than later.”

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

NOVEMBER 2018 || DDNEWS 25
Attaining adhesion

KB103 yields functional collagen production and sustained wound healing in chronic blistering patients

BY KELSEY KAUSTINEN

PITTSBURGH—October saw gene therapy company Krystal Biotech Inc. share interim results from an ongoing placebo-controlled Phase 1/2 clinical trial of KB103 in dystrophic epidermolysis bullosa (DEB). DEB is an incurable and often fatal skin blistering condition that results from a lack of collagen in the skin—specifically type VII collagen, or COL7—due to genetic mutations. Given that COL7 is key in anchoring fibrils, which connect the dermis and epidermis, the lack of this protein causes blisters to form in the dermis as it separates from the epidermis. KB103 is a replication-defective, non-integrating viral vector designed with KrystalStar-D platform. It delivers functional human COL7A1 genes directly to dividing and non-dividing skin cells using HSV-1, a paracrine vector that can penetrate skin cells more effectively while carrying a high payload and presenting with low immunogenicity.

The trial in question consists of two recesive DEB, NCI[+1] patients ages 25 and 28, who were treated with topical KB103 and re-dosed. Each patient had two wounds with a surface area of approximately 10 cm² randomized to be treated with either topical KB103 or placebo, and also received intra-dermal injections of the compound to intact skin to monitor its mechanism of action. Following administration, the treated wound and injected intact skin were biopsied to measure COL7 expression and anchoring fibril formation, as well as being evaluated for healing compared to the placebo-treated wounds and baseline.

IN THIS SECTION
- Dermatology/ Wound healing/Gene therapy
- Attaining adhesion
- Oncology
- Phase 1 results
- Therapy Triumph
- Trial management
- Recruitment in the digital age (DIGITAL from cover)
- Veeva announces new clinical trial management offering
- Trial initiation and advancement
- Out of the starting gate

For more information, visit www.DDN-News.com
Both patients met all primary efficacy endpoints in topically treated wounds, which included presence of functional COL7 expression, observation of NC1 and NC2 reactive anchoring fibrils and continued expression after repeat administration. In addition, safety endpoints—no adverse events, inflammation or irritation—were also met.

“With multiple applications of the topical therapy, we saw no inflammation, no systemic symptoms,” Dr. Peter Marinkovich, an associate professor of dermatology at Stanford University and principal investigator in the GEM study, said in a conference call. “We saw no shedding in the blood or urine samples that we collected, and no antibodies to COL7 were detected. Inherent in this therapy is the fact that it does not randomly incorporate into the genome, so unlike other viral therapies, this therapy has no risk of insertional oncogenesis.”

The treated wounds showed robust functional COL7 expression via immunofluorescence in biopsy samples by the second day of treatment, with functional expression measured by staining tissue samples with NPI185 and LH24 antibodies, which bind to NC1 and NC2 domains of the COL7 protein, respectively. Both patients were NC1 positive at baseline, and their biopsy samples showed NC1 and NC2 domains, proof of production of functional COL7. Immunoelectron microscopy showed NC1 and NC2 reactive anchoring fibrils in both patients by day 14.

According to Marinkovich in the call, “It’s estimated that collagen 7 half-life is about two months in vivo in human skin, and so the expectation is that when we see linear staining for COL7, this is going to remain durable over a month’s time point,” says Dr. Peter Marinkovich of Stanford University, seen here at left with colleagues and an epidermolysis bullosa patient.

The topically treated wounds closed in two weeks, and were still closed by the time of Krystal’s announcement. In the placebo-treated wounds, closure took 10 weeks in Patient 1, while Patient 2’s placebo-treated wounds had not completely closed through the course of the study. Both patients’ KB103-treated wounds remained closed as of mid-October, which comes to 4.5 months of total closure for Patient 1 and 3.5 months for Patient 2.

“Many trials in EB today are looking at wound healing, and there are a number of different types of ways that EB wounds can heal, with either allogeneic treatments, as well as wound care improvements,” Marinkovich explained in the company’s conference call. “However, the real key is to look at durability of wound closure, as epidermolysis bullosa is not a defect of re-epithelialization. The keratinocytes in the epithelium can cover the wound. The problem is adhesion, or maintenance of epithelium on the wound, and the danger of re-blistering after the wound has healed. Many of these patients have repeated healing and wounding occurring continuously, and it’s a cycle that can be broken by adding adhesion to the epidermis. That’s what this therapy seeks to do, is to add adhesion to the epidermis.”

Krystal has submitted the clinical data to the FDA, and the protocol for future patients in this Phase 1/2 trial has been amended to remove the intradermal arm. Additionally, the protocol moving forward will enroll pediatric patients, and will examine the durability of wound closure resulting from KB103 to aid in determining endpoints for a Phase 3 trial. The updated protocol also allows for increased administration to larger wound areas.

“Results on 2 patients demonstrate a meaningful clinical benefit and suggest that KB103 can afford a simple, convenient, painless way to administer treatment for patients suffering with this debilitating disease,” Marinkovich commented in a press release. “These early data are encouraging, and we look forward to continuing the study in pediatric populations.”

"It’s estimated that collagen 7 half-life is about two months in vivo in human skin, and so the expectation is that when we see linear staining for COL7, this is going to remain durable over a month’s time point,” says Dr. Peter Marinkovich of Stanford University, seen here at left with colleagues and an epidermolysis bullosa patient.
**Digital**

**CONTINUED FROM PAGE 1**

Better understand patient perceptions surrounding online clinical trial advertising. Syenos says it is "continually identifying key insights to deliver meaningful communications to shorten the distance from lab to life," and the research evaluated patient trust levels for different digital advertising channels, such as social media, TV, and email. This research helps to identify key areas for improvement and to develop targeted strategies to increase patient trust and engagement.

**CONTINUED FROM PAGE 26**

Cell response in peripheral blood and increased CD8+ T-cell response to epitope-recognizing tumor cell lines, said Inovio.

According to Dr. J. Joseph Kim, Inovio’s president and CEO, “We remain committed to supporting early-onset celiac disease patients, and this new partnership with GEN3 is a significant step forward in advancing Nexvax2 to protect celiac patients from the effects of inevitable gluten exposure.”

Enrollment begins with MED2002 for erectile dysfunction

**GATE**

**CONTINUED FROM PAGE 26**

We are excited to continue demonstrating CV’s1 potential in multiple clinical indications, particularly in a treatment setting in which checkpoint inhibition alone has yet to show significant benefit. The combination of a chemotherapeutic agent with a checkpoint inhibitor could result in a novel approach to fighting colorectal and pancreatic cancers, which are among the most difficult-to-treat malignancies to date,” said Paul Chaplin, president and CEO of Bavarian Nordic.

**First patient treated with ILB for ALS**

VIKEN, Sweden—On Nov. 2, TikoMed AB, a specialty pharma company focused on developing therapeutics for treating acute and degenerative neurological diseases, announced that the first patient who recently had amyotrophic lateral sclerosis (ALS) has been treated with the company’s investigational drug ILB, in the ongoing clinical trial at Sahlgrenska University Hospital in Gothenburg, Sweden.

Anders Kristensson, CEO of TikoMed, commented, “With ILB, we present a potentially new class of drug which can address the underlying causes of neurodegeneration, as seen in a chronic disease such as ALS. We are committed to bringing ILB through our ALS clinical trial program and hopefully one step closer to ALS sufferers battling this fatal disease.”

TikoMed will also be running a Phase 1b study in collaboration with Birmingham University in Birmingham, UK. In this trial, 15 patients with ALS will receive ILB for a 20-week treatment period.

**Archier-1 trial of Betalutin plus rituximab begins dosing**

OSLO, Norway—This fall saw Nor- dan-Norwegian ASA announced that the first patient had been dosed in the Archier-1 trial investigating Betalutin (177Lu-satetaxel- etan-Idolomab) in combination with rituximab (RTX) in secondary progressive multiple sclerosis (2L PL).

Rituximab is a CD20-targeting monoclonal antibody that is administered to patients with newly diagnosed or relapsed FL as a single agent or in combination with chemotherapy. Over time, patients may develop resistance to RTX, so alternative targets are important. In addition, developing novel “chemo-free” regimens for patients as an alternative to chemotherapy is desirable.

Edardo Bravo, Nordic Nan- vector CEO, commented, “Archier-1 presents an opportunity to investigate the potential of a novel dual CD73/CD20-targeting combination approach in 2L FL patients. If the preclinical results translate to patients, this may indicate a new way to administer biologic therapy in FL.”

**Phase 2 enrollment begins for celiac disease vaccine in Australia and New Zealand**

CAMBRIDGE, Mass.—In late October, ImmusanT Inc., a clinical stage company leveraging its Epitope-Specific Immuno-Thera- py (ESIT) platform to deliver in-class peptide-based immuno- modulatory vaccine therapies to patients with autoimmune diseases, initiated enrollment in Australia and New Zealand for its Phase 2 RESET CeD study.

This trial will assess the safety, tolerability and efficacy of the company’s lead therapeutic candidate, Nexvaxa, in patients with celiac disease who carry the immune recognition genes for HLA-DQ2.5. The study targets an estimated 90 percent of the celiac patient population, and Nexvaxa is designed to protect these patients from the effects of gluten exposure.

“Initial early development of Nexvaxa took place in Austra- lia and New Zealand, and we are thrilled to be expanding our recently launched Phase 2 trial to patients from regions that have been with us from the begin- ning,” said Leslie Williams, CEO of ImmusanT. “With increasing gluten exposures that can significantly affect health and long-term negative impacts on patient health. At ImmusanT, we are deeply committed to advancing Nexvaxa to protect celiac patients from the effects of inevitable gluten exposure.”

Enrollment begins with MED2002 for erectile dysfunction

**GUILDFORD, U.K.—Futura Med- ical plc, a pharmaceutical company developing a portfolio of innovative generic products based on its proprietary transdermal DermaSys drug delivery technology, recently reported that its first patient had entered the first European Phase 3 study (FM57), of MED2002, a topical glycy- erol triinitrate (GTN) gel for the treatment of erectile dysfunction (ED). The Phase 3 study remains on track, with headline data expected by the end of 2019.

“We are pleased to announce the first patient enrollment in our first European Phase 3 trial with MED2002. This is an important milestone for Futura, building on the success of both Phase 1 and Phase 2 data,” noted James Barder, CEO of Futura Medical. “Futura is now in a position to build value by progressing the development of MED2002 through its planned Phase 3 studies, and we are excit- ed to be moving closer to bringing an innovative, highly differenti- ated ED product to market that could help the many ED patients whose needs are not met by cur- rent treatments.”

**EDITCONNECT:** E111819

**INOVIO**

**CONTINUED FROM PAGE 26**

CCT offers what Advanced Clini- cal calls “an innovative approach” to conducting clinical research for the prevention and treatment of Alzheimer’s disease, saying that CCT has created a new research model that addresses the two obstacles facing this research cate- gory. Specifically, this model brings clinical trials directly to patients who may otherwise be unable to participate due to travel, scheduling or health con- ditions by embedding a clinical research infrastructure within established senior living communi- ties. The infrastructure includes a clinic staffed by physicians, clini- cal research coordinators and other research professionals.

“As CCT’s only CRO partner, we are excited to offer our custom- ers direct access to this patient population through our collabora- tion,” said Julie Roes, president of Advanced Clinical, a clinical devel- opment organization providing contract research, functional ser- vices and project management for long-standing recruitment roadblocks in Alzheimer’s clinical trials. This new partnership is expect- ed to enable Advanced Clinical to develop a new research model by reviewing patients’ access to trials and enhancing Alzheimer’s patient recruitment and retention for sponsors.
BY KELSEY KAUSTINEN
SAN DIEGO—San Diego is known for its beaches, the famous Gaslamp Quarter and warm weather year-round, but in December one of the biggest draws will be the 2018 ASCB | EMBO Meeting, which will run from Saturday, Dec. 8, through Wednesday, Dec. 12. This is the 58th meeting of the ASCB, and the second year that the American Society for Cell Biology (ASCB) and the European Molecular Biology Organization (EMBO) have hosted this joint event. Co-chaired by Thomas Langer of the Max Planck Institute for Biology of Aging and Samara Reck-Peterson of the University of California, San Diego/HHMI, this year’s meeting promises to be “packed with opportunities to learn from and network with the world’s leading cell biologists,” according to ASCB.

The 2018 ASCB | EMBO Meeting represents the second year that the American Society for Cell Biology and the European Molecular Biology Organization have collaborated for a joint event. Pictured here are some participants in the 2017 meeting, which was held in Philadelphia.

ASCN | E.M.B.O.
CONTINUED ON PAGE 30

The 2018 ASCB | EMBO Meeting describes the Doorstep Meeting this way: “This doorstep symposium features leaders in stem cell biology who have studied mechanisms by which stem cells respond to stress. One of the most interesting areas of stem cell biology concerns the mechanisms by which stem cells withstand stresses such as tissue injury. So far, most studies of stem cell function have been in normal tissues. Less is known about the mechanisms that maintain stem cells in damaged tissues. Replicative stress and the need to regenerate differentiated cells can deplete stem cells, requiring the induction of distinct mechanisms that ensure stem cell persistence beyond homeostasis.”

The meeting will provide an overview of the field, with significant time allotted for discussion and interaction between audience and ASCB/EMBO.
**Keynote Lecture and Symposia**

**Keynote Lecture**
SATURDAY, DEC. 8, 6 P.M.
• ‘Niches for Stem Cells in Bone Marrow” by Sean J. Morrison, Children’s Medical Center Research Institute, UT Southwestern/HMRI

**Symposium 1: Nuclear Organization**
SUNDAY, DEC. 9, 8 A.M.
• “Genome Architecture Mapping (GAM): Discovering 3D Chromatin Contacts in Rare Cell Types” by Ana Pombo, Belin Institute for Medical Systems Biology
• “Super-resolution Imaging of Transcription in Living Mammalian Cells” by Ibrahim Cissé, Department of Physics, Massachusetts Institute of Technology
• “Mechanisms of Transcriptional Bursting” by Arun Raj, University of Pennsylvania

**Symposium 2: Cell Migration**
SUNDAY, DEC. 9, 9:45 A.M.
• “Principles of Leukocyte Locomotion and Navigation” by Michael Sait, IST Austria
• “Imaging Leukocyte Dynamics In Vivo” by Anna Huttunen, University of Wisconsin, Madison

**Symposium 3: Neuronal Cell Biology**
SUNDAY, DEC. 9, 9:45 A.M.
• “Disturbance of Phase Transitions in Neurological Disease” by J. Paul Taylor, St. Jude’s Children’s Research Hospital/HMRI
• “Dynamics of Autophagy in Neuronal Homeostasis and Neurodegeneration” by Erika Holzbaur, University of Pennsylvania

**Symposium 4: Cytoskeletal Dynamics**
MONDAY, DEC. 10, 8 A.M.
• “Control of Cell Architecture by Microtubule Minus-End Binding Proteins” by Anna Ahkmanova, Utrecht University
• “The Dynein/Dynactin Complex and Long-Distance Transport” by Andrew Carter, MRC Lab Molecular Biology
• “Multi-component Mechanisms Controlling Actin Dynamics” by Bruce Guohe, Brandeis University

**Symposium 5: Metabolism**
MONDAY, DEC. 10, 9:45 A.M.
• “Metabolic Transitions in Cancer: Lessons from Viral Infection” by Heather Christofk, University of California, Los Angeles
• “Mechanisms and Physiology of Lipid Storage in Lipid Droplets” by Robert Farese, Jr., Harvard School of Public Health and Harvard Medical School

**Symposium 6: Regeneration and Morphogenesis**
MONDAY, DEC. 10, 9:45 A.M.
• “Ly6G Stem Cell-Based Organoids in Human Disease” by Hans Clevers, Hubrecht Institute, Royal Netherlands Academy of Art and Sciences, University Medical Center Utrecht, Princess Maxima Center for Pediatric oncology
• “Building the Mouse and Human Embryo In Vivo and In Vitro” by Magdelena Zernicka-Goetz, University of Cambridge

**Symposium 7: Organelle Communication**
TUESDAY, DEC. 11, 8 A.M.
• “The Role of ER Membrane Contact Sites in Lipid Metabolism and Organelle Biogenesis” by Wil Prinz, National Institute of Diabetes and Digestive and Kidney Diseases, NIH
• “In TOR and Lysosomes in Growth Control” by David M. Sabatini, Whitehead Institute for Biomedical Research, Broad Institute, MIT/HMRI
• “New Insights into Mitochondrial Vesicle Transport” Heidi McBride, Department of Neurology and Neurosurgery at McGill University

**Symposium 8: Quality Control**
WEDNESDAY, DEC. 12, 11:20 A.M.
• “Ribosome Rescue and Homeostasis in Health and Disease” by Rachel Green, Johns Hopkins University School of Medicine/HMRI
• “Targeting the Cell’s Stress Pathways for Therapeutic Benefit” by Peter Walter, University of California, San Francisco

**ASCB/EMBO**
continued from page 29

speakers, with the goal of inspiring the ASCB community to tackle the cell biology of stem cells and tissue regeneration.”

In addition to the Doorstep Meeting, this year’s conference features a number of symposia and subgroup meetings, as well as three scientific workshops that will run concurrently on the days of the symposia. All told, more than 2,700 poster presentations are expected this year, offering attendees no end of new research topics to explore.

For student attendees, there will be a one-day course for graduate and postdoctoral students on Fri.

day, Dec. 7, at Biocom in La Jolla, Calif., before the official ASCB/EMBO meeting begins. Hosted by ASCB and the Keck Graduate Institute (KGI), the 2018 Biotech Mini-Course runs from 8 a.m. to 5 p.m. and will offer guidance for students in making themselves more competitive in the job market. The deadline to apply for participation is Nov. 15, and it is not necessary to register for the 2018 ASCB/EMBO Meeting to attend the one-day course.

From 8 a.m. to noon, Dr. Steve Casper, Dean of the School of Applied Life Sciences and Henry E. Riggs Professor of Management at KGI, will lead the “Introduction to Bioscience Business” morning session. According to ASCB, this session will familiarize students with the dynamics and commercialization processes of the bioscience industry, exploring common business strategies and how research is translated into industry ventures.

Lectures will be combined with discussions based on Harvard Business School teaching cases from the industry. A networking lunch will run from noon to 2 p.m., during which students will have the chance to speak with representatives from local biotech companies.

From 2 p.m. to 5 p.m., Dr. Randall Ribaudo and Larry Petcovic, co-founders of SciPhD, will present “The Business of Science—the higher order chromatin organization in eukaryotic cells.” Sun-
day, Dec. 9, will see a panel event at the Omni Hotel Salon from 7 p.m. to 9 p.m., hosted by HHMI. This event is part of an international effort to find a scientist—or a team—to head up a new research area at Janelia centered on the life sciences, technology development or a mix of both focal points. Those interested can find more information at https://www.janelia.org/janelia/research/competition/opportunity. And on Wednesday, Dec. 12, an event supported by the Gordon and Betty Moore Foundation will combine the cellular focus of the ASCB/EMBO Meeting and the coastal influence of San Diego in “Genetic Tool Development in Marine Protists: Emerging New Model Organisms for Cell Biology.” This will be a three-hour event, running from 2 p.m. to 5 p.m. in the Santa Rosa Room at the Marriott Marquis, and will offer posters, presentations and discussion surrounding work in developing new model systems in the field of marine protists.

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

**The 2018 ASCB | EMBO Meeting will offer a variety of programming, including poster presentations, workshops, symposia and satellite events. Above, attendees at the 2017 meeting take in a demonstration.**
Mount Sinai recognized for excellence in mitochondrial care

NEW YORK—The Icahn School of Medicine at Mount Sinai has been recognized as a certified Mitochondrial Medicine Center by the Mitochondrial Care Network, a newly established collaborative founded by four national mitochondrial disease advocacy groups. The certification recognizes centers for dedication to mitochondrial medicine. Drs. Pankaj Prasad and Bryant Webb, co-directors of the Mitochondrial Medicine Program at Mount Sinai, were also cited as leaders in this field of care.

The Mitochondrial Care Network was formed to formally unify clinicians who provide medical care to individuals with mitochondrial disease; define, design and implement best practices in mitochondrial medicine; and optimize management and care for affected patients. Factors considered by the Network include current and prior patient volume, multidisciplinary approach and hospital/care center support.

The Mitochondrial Medicine Program at the Mount Sinai Genetics Faculty Practice combines cutting-edge research, state-of-the-art diagnostics and novel therapies to provide comprehensive disease evaluation, counseling and management for patients suspected to be diagnosed with mitochondrial disease.

We are honored to join this world-class group of clinicians and institutions to share our experiences and ideas with,” said Webb. “In addition to being a hub of support, we hope this newly formed network will help raise awareness about the prevalence of mitochondrial disorders.”

“Collaborative medicine has time and time again exemplified strength in numbers,” said Prasad. “By leveraging both our partnership with the Mitochondrial Care Network and Mount Sinai’s legacy of genomic research and clinical care in genetics, we hope to bring our pioneering ideas to life and improve the standard of care for those with mitochondrial disease.”

HUMAN CELL MODELS COULD POTENTIALLY REPLACE ANIMAL EXPERIMENTS

CAMBRIDGE, U.K.—Elpis Biomed Ltd., a University of Cambridge spinout developing high-quality human cells via its proprietary OPT-X platform, announced recently that life-sciences entrepreneur Dr. Jonathan Milner, deputy chairman and founder of Abcam, mentioned the company, stating: “Elpis human cells can fix the broken drug discovery process by replacing animal experiments,” during his plenary lecture at the recent European Laboratory Research & Innovation Group (ELRIG) Drug Discovery Conference.

During his plenary address, titled “Opportunities in the Golden Age of Biology,” Milner asked whether the drug discovery process is “broken,” explaining: “Over the past decades, the return on investment on pharmaceutical research and development has suffered exponential decline. A main contributor to the rising costs of drug development and failure rates, both at the pre-clinical and clinical stage. The causes for drug failure are likely due to the biological differences between the current animal models and cell lines used for drug discovery and human biology. The solution to this problem is to integrate human cell models early into the drug development process.”

Although human cells are better models for drug screening, few were featured at the ELRIG conference, and Milner noted that “the lack of human cell models being utilized boils down to the fact that the current technology for generating patient derived cells does not meet the requirements for drug screening.” Elpis, backed by Milner’s personal investment, “provides the first robust and scalable, biologically relevant cell models for drug development,” he added.

Dr. Mark Kotter, scientific founder of Elpis, said, “Elpis’ mission is to make human cells easy. Our proprietary OPT-X technology allows us to produce human cells of unprecedented quality, purity, and consistency. We are developing a wide range of cell products to support the research, drug discovery and cell therapy communities, and are delighted that our technology has been brought to the attention of an audience of drug discovery experts by an industry heavyweight like Dr. Milner.”

The benefits of on/off control over CAR-T

CALIFORNIA—Calibr, a nonprofit drug discovery division of Scripps Research, recently announced findings from a new study that show its proprietary switchable chimeric antigen receptor (CAR) T cells may offer therapeutic advantages in addition to being employed as a safety mechanism.

Calibr’s switchable CAR-T cell platform was first reported in 2016 and uses antibody-based switches to control the activation and targeting of the engineered CAR-T cells. This has been previously demonstrated to act as a safety switch by disrupting the level of activity to be titrated, or tuned up or down, thus potentially avoiding complications from excessive cytokine release or cytokine storm.

A new paper titled “Switchable control over in vivo CAR-T expansion, B cell depletion, and induction of memory” that was published in the Proceedings of the National Academy of Sciences November issue, now goes beyond these initial findings to demonstrate a therapeutic benefit to switches.

“Conventional CAR-T cell therapies typically involve a single infusion of the engineered T cells, which exponentially expands within the patient, and then contracts over time,” said corresponding author Dr. Travis S. Young, vice president of biologics at Calibr. “Our approach mimics a more natural behavior of a T cell, in that the CAR-T cells are turned on and off in a cyclical fashion, which affords defined expansion and contraction of the CAR-T cell population. Through this, we discovered that the ‘off’ period is highly beneficial—perhaps even more so than the ‘on’ period—for engrafting a robust central memory population.”

The study could have important implications for the rapidly expanding field of CAR-T cell therapies, which harness the power of a cancer patient’s own immune system to attack and destroy cancer cells. While they have delivered remarkable results in late-stage blood cancers that failed to respond to other treatments, not all patients experience a complete and durable response. A significant number also suffer serious adverse events, including cytokine release syndrome, which occurs at the peak of CAR-T cell expansion.”
Biogen boosts multiple sclerosis research

Evidence supports serum neurofilament light as useful biomarker; Biogen and Siemens to develop blood test

BY MEL Y. YEATES
CAMBRIDGE, Mass.—October has been a busy month for Biogen, with data from research showing that serum neurofilament light (sNfL) is a potential biomarker of disease activity and treatment response in multiple sclerosis (MS) disease progression, which could provide physicians with real-world evidence to help inform treatment decisions.

As well, results from MS PATHS (Multiple Sclerosis Partners Advancing Technology and Health Solutions) are supporting the use of technology to monitor for clinically important outcomes, including cognitive changes.

And new analyses of ongoing studies continue to support the long-term benefits of Tecfidera (dimethyl fumarate) and Tysabri (natalizumab), particularly when starting treatment early within the disease course.

These findings were recently presented at the 34th Congress of the European Committee for Treatment and Research in MS (ECTRIMS) in Berlin.

Biogen is currently researching sNfL, a protein that is expressed in neurons and found in elevated levels in the blood of people with MS, as a biomarker of disease activity. Results from a retrospective analysis of more than 1,000 patients support the clinical relevance of sNfL levels in need to predict disease severity and monitor treatment response. Data indicate that sNfL levels above a certain threshold are associated with ongoing disease activity and negative clinical and radiologic outcomes, such as disability progression and brain atrophy.

Researchers also found that introducing disease-modifying therapies significantly reduced sNfL levels, which in turn is associated with better treatment outcomes.

As Dr. Bernd C. Kieseier, head of the Global MS unit of Biogen, tells DDNews, “Biogen is actively collaborating with academic leaders in this field to better understand the clinical and research utility of this promising biomarker. There are currently no blood biomarkers for treatment monitoring in MS. The data presented at ECTRIMS support the clinical relevance of sNfL levels in the blood to predict disease severity and monitor treatment response.

In a study of samples from over 1,000 patients, the company’s VeriStrat test was found to be a significant predictor of outcomes (independent of ECOG Performance Status categories), patient EGRF mutation status, treatment received and other clinical variables. The study showed that patients who presented with VeriStrat Poor results and better ECOG PS had worse overall survival than patients with VeriStrat Good results and a worse PS. VeriStrat also proved capable of predicting response differences in EGRF mutation-positive patients and EGRF wild-type patients. EGRF mutation-positive patients with a VeriStrat Good result saw improved overall survival compared to VeriStrat Poor patients when treated with a single-agent EGRF-tyrosine kinase inhibitor (EGFR-TKI), which held true when a combination of two EGRF-TKI therapies were administered.

VeriStrat Poor patients performed better on the combination regimen than on erlotinib alone.

**Targeted TMB assessment**

MolecularMD validates Thermo Fisher assay that can help in trial stratification

**BY ILENE SCHNEIDER**
PORTLAND, Ore.—MolecularMD, a diagnostics company that enables the development and commercialization of precision medicines in oncology, has validated Thermo Fisher Scientific’s Oncomine Tumor Mutation Load (TML) Assay for clinical research trials to facilitate immunotherapy drug development programs for the pharmaceutical industry.

Tumor mutation burden (TMB) analysis, often described as the latest approach in immuno-oncology, is becoming an independent predictor for patient stratification and response to immunotherapies, such as checkpoint inhibitors.

The Oncomine Tumor Mutation Load Assay is available to MolecularMD’s clients involved in translational research and clinical trials. The company is doing additional studies to determine the clinical utility of TMB analysis for predicting patient response to checkpoint inhibitors.

According to Dr. Cindy Spittle, vice president of development and scientific affairs at MolecularMD, “The methods used so far to assess tumor mutation burden in clinical studies have included whole-exome sequencing and several laboratory-developed, targeted next-generation sequencing panels, but in order to fully determine the value of TMB as a predictive biomarker, a standardized panel, workflow and data analysis pipeline for TMB assessment is needed.”

She added, “The Oncomine Tumor Mutation Load Assay is unique in that it is the first commercially available assay that is designed for assessing TMB in formalin-fixed paraffin-embedded (FFPE) samples that can be validated by a clinical laboratory for use as a laboratory-developed test. Since the reagents and software are provided for the end to end workflow, labs that adopt the method will be able to provide standardized TMB analysis. The TML Assay is also unique in that the UC Davis and NeuroPointDX to launch biomarker panel

New test will target autism diagnosis for children as young as 18 months

**BY LORI LESKO**
SACRAMENTO, Calif.—With an aim of launching a new biomarker test panel that could offer the first objective test leading to the earliest diagnosis of autism spectrum disorder (ASD) thus far, investigators at the MIND Institute...
cognitive function using elements of that, according to Kieseier, “evaluates assessment of cognitive function of MS cognitive screening tests. The bol Digit Modalities Test, regarded after and validated against the Sym-int MS PATHS, CogEval is modeled like the Processing Speed Test used in the United States, Europe, Canada, cognition in their patients, Biogen MS PATHS network easily assess changes in MS. ”

“Research shows that introducing disease-modifying therapies significantly reduces sNfL levels,” says Kieseier. “In the retrospective analysis, researchers found that sNfL levels were significantly lower in patients taking Plegridy or Tysabri compared to those taking placebo, with the most pronounced effects observed with Tysabri. Treatment with Tysabri reduced sNfL levels below the identified threshold in 96 percent of patients.”

“The research we presented at ECTRIMS not only reflects our proven record of developing innovative medicines for MS, but also our pursuit of new clinical avenues aimed at generating data that we believe will lead to greater precision medicine in MS. New analyses of ongoing studies presented at ECTRIMS continue to support the long-term efficacy and well-characterized safety of Tecfidera and Tysabri, particularly when used early within the disease course.”

MRI in characterizing and monitoring the differential evolution of tissue injury in individuals with MS. Biogen has expanded its collaboration with Siemens Healthineers to develop an sNfL blood test as an additional tool to monitor MS. A highly sensitive, robust and validated assay will allow researchers to measure sNfL levels in the blood of MS patients with the goal of better understanding disease activity and monitoring treatment response.

Dr. Peter Calabresi, director of the Division of Neuroimmunology and Neuro-infectious Diseases at the Johns Hopkins University School of Medicine, said, “These findings support sNfL as a clinically useful biomarker to help predict whether a person with MS is likely to have a fast-progressing or milder disease course. They also open the possibility of using a simple blood test to monitor whether a patient is responding to a specific treatment. The strong predictive power of sNfL may ultimately provide physicians with additional information beyond what is currently measured by MRIs to help guide treatment decisions.”

On the technological side of things, the MS PATHS collaboration of 10 leading MS centers in Europe and the United States, along with Biogen, uses technology in routine care to collect clinical, MRI and biologic data from patients in real time at the point of care. Using an iPad-based assessment, researchers are able to broadly monitor for changes in motor, visual and cognitive function.

Cognitive deficits affect over half of people living with MS, but aren’t regularly assessed in clinical practice and can be difficult to quantify. “New MS PATHS data presented at ECTRIMS demonstrates that cognitive decline is as prevalent as physical decline in people with MS, but can occur independently from physical symptoms,” notes Kieseier. “In fact, cognitive decline occurred independently from physical symptoms in approximately 75 percent of patients in the study. These results underscore the importance of monitoring cognition in routine care and the need for effective treatment strategies for cognitive changes in MS.”

To help physicians outside of the MS PATHS network easily assess cognition in their patients, Biogen has developed CogEval, a free app available to healthcare providers in the United States, Europe, Canada, Japan, Australia and New Zealand. Like the Processing Speed Test used in MS PATHS, CogEval is modeled after and validated against the Symbol Digit Modalities Test, regarded by many experts as the gold standard of MS cognitive screening tests. CogEval provides an iPad-based assessment of cognitive function that, according to Kieseier, “evaluates cognitive function using elements of attention, psychomotor speed, visual processing and working memory. During the two-minute assessment, the patient pairs abstract symbols with numbers, using a key as a guide. CogEval can be used by MS specialists anywhere at any time.”

Finally, results from the ENDORSE study demonstrate that the clinical benefits of Tecfidera in reducing MS relapses and disability progression in newly diagnosed patients were maintained throughout nine years of continuous Tecfidera treatment, with relapse rates remaining low and more than 90 percent of patients maintaining walking abilities. Analysis from the Tysabri Observational Program (TOP), the largest ongoing real-world study of Tysabri-treated patients, reinforces the long-term safety and consistent effectiveness of Tysabri over 10 years, especially for patients with minimal or mild disability and those who were previously treated with fewer disease-modifying therapies.

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“It is unlikely that a single marker will detect all autism. This paper demonstrates that alterations in metabolic profiles can detect sizable subsets of individuals with autism.”

David G. Amaral of the UC Davis MIND Institute applied, the better the outcome.” CAMP researchers believe the answer lies in the metabolome—the molecules that remain after larger molecules have been broken down (metabolized). Metabolomics has the advantage of monitoring both genetic and environmental contributions to the development of autism. “By the time you’re getting to metabolomics, you’re looking at how the body is working, not just the genes it has,” Amaral explains. “The team hopes to use these and other CAMP findings to accelerate a diagnosis and move kids into intensive behavioral therapy at an earlier age.”

“Unlikely that a single marker will detect all autism,” says David G. Amaral, founding director of research at the MIND Institute and senior author on the journal paper. “This is the first of hopefully many panels that will identify other subsets of kids with autism.”

“Though a 17 percent subgroup may seem small, it is actually quite significant,” Amaral says. “ASD encompasses a complex array of symptoms, and no one expected to find a single group of markers that would diagnose all subsets. Rather, researchers hope to create a number of metabolic assays that cover all variations.”
NEC and Transgene collaborate on individualized cancer immunotherapy

The companies will cooperate in clinically assessing the predictive capabilities of NEC’s artificial intelligence and the therapeutic potential of Transgene’s myvac MVA-based viral vector platform in an individualized immunotherapy for the treatment of solid cancers.

EDITCONNECT: E10301801

By the skin of their addiction

Research team finds that skin grafts protect mice from lethal cocaine doses.

EDITCONNECT: E10101802

What you may have missed online from DDNews

Mayo Clinic researchers identify glioblastoma “ground zero”

Mount Sinai researchers found that deactivating the protein TEAD1 could make it possible to stop glioblastoma tumor cells from spreading.

EDITCONNECT: E10091801

Evotec continues building BRIDGEs

Company announces new drug discovery collaboration with Sanofi under its BRIDGE initiative program.

EDITCONNECT: E10101804

Cancer Genetics and Cellaria team up to create precision medicine tools

Collaboration will focus on pharmacology models to support biopharma R&D with a goal of developing new cancer therapeutics.

EDITCONNECT: E10101801

CavoGene licenses SynCav1 for CNS disorders

The novel investigational gene therapy could help patients with amyotrophic lateral sclerosis, Alzheimer’s disease, traumatic brain and spinal cord injury, and age-related cognitive decline.

EDITCONNECT: E10231801

Evotec continues building BRIDGEs

Company announces new drug discovery collaboration with Sanofi under its BRIDGE initiative program.

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Positive Phase 2b nemolizumab results from Galderma

Galderma announces positive results from Phase 2b study of nemolizumab in patients with moderate-to-severe atopic dermatitis.

EDITCONNECT: E10111801

A new clinical collaboration for B cell malignancies

MEI Pharma and BioGenne announce collaboration to evaluate ME-401 in combination with Zanubrutinib in patients with B cell malignancies.

EDITCONNECT: E10111801

A protein marker for cancer recurrence

Mount Sinai team reports that the presence or absence of protein NR2F1 can indicate whether a patient’s cancer cells are dormant or likely to relapse.

EDITCONNECT: E10121801

Karuna Pharmaceuticals Inc.

Steven Paul
Chief Executive Officer

BOSTON—In August, Karuna, a company focused on targeting muscarinic cholinergic receptors for the treatment of neuropsychiatric disorders marked by psychosis and cognitive impairment, announced Dr. Steven Paul as CEO.

“Targeting muscarinic receptors is one of the most promising approaches to treating both the psychosis and cognitive impairment that characterize many disabling neuropsychiatric disorders, including schizophrenia and Alzheimer’s disease, where there is a profound need for more effective treatments,” Paul said.

“Having been one of the scientists involved in the original work on xanomeline at Lilly, I am excited by the progress that Karuna has made to unlock this important new class of therapeutics. I am looking forward to helping Karuna become a leader in the field and believe in the potential for KarXT to be the first antipsychotic drug with a truly novel mechanism in over 60 years. We are also excited by recent preclinical work suggesting that KarXT may be an effective non-opiate treatment for pain.”

Vasomune Therapeutics

Douglas A. Hamilton
President and CEO

TORONTO—Vasomune, a biotechnology company developing therapeutics targeting vascular dysfunction and inflammation, recently announced that Douglas A. Hamilton had been appointed president and CEO of the company.

“I am delighted to be joining Vasomune and its team of founders, dedicated scientists, consultants and high-profile institutional investors,” said Hamilton. “By selectively targeting the host response, Vasomune’s therapeutic approach focuses on a single, non-redundant pathway that inhibits multiple factors responsible for driving runaway inflammatory processes.”

Most recently, Hamilton served as president and CEO of MetaStat Inc., a precision medicine company discovering and developing novel anti-metastatic drugs for the treatment of patients with aggressive cancer.

Principia Biopharma

Dolca Thomas
Chief Medical Officer

SOUTH SAN FRANCISCO, Calif.—October saw Principia, a clinical-stage biopharmaceutical company focused on immunology and oncology, name Dr. Dolca Thomas as its chief medical officer. Thomas brings approximately 15 years of industry and medical experience to Principia and joins the company from Roche, where she was vice president and global head of translational medicine for immunology, inflammation and infectious disease.

“I am impressed with Principia’s approach to BTK inhibition in autoimmune disease and believe that application of the company’s proprietary Tailored Covalency platform may be applicable across a wide range of autoimmune and inflammatory conditions,” said Thomas. “I have been involved in more than a dozen immunology product candidates, and I look forward to contributing to the potential success of Principia’s pipeline assets and moving the company towards late-stage clinical development.”
Focus Feature: CRISPR technology

Companies and academic institutions work together to unlock cellular reprogramming, single cell RNAseq-linked screening, stem cell-derived therapies for diabetes, engineered mammalian cell lines and more.

"Fate Therapeutics was founded on a commitment to innovation in the field of iPSC technology, and we will continue to invest in exciting new technologies that extend our dominant leadership position in the development of off-the-shelf, iPSC-derived cell products," said Scott Wolchko, president and CEO of Fate Therapeutics. "Dr. Ding was instrumental in successfully pioneering the use of small molecules to engineer iPSCs and the building of our iPSC product platform, and we look forward to advancing this novel CRISPR gene activation approach for cellular reprogramming."

CRISPR can precisely edit the genome by targeting a unique sequence of DNA, but in this case Ding repurposed CRISPR to enable target gene activation, allowing regulation of endogenous gene expression. His research team showed that targeting a single location of the genome using CRISPR genome activation could trigger iPSC generation. The findings were published in an article entitled "CRISPR-Based Chromatin Remodeling of the Endogenous Oct4 or Sox2 Locus Enables Reprogramming to Pluripotency," in the journal Cell Stem Cell in January 2018.

Fate Therapeutics is using clonal master iPSC lines to overcome the complexity, heterogeneity and substantial costs associated with sourcing cells from a patient or an allogeneic donor. Instead, iPSC-derived cell products can be consistently and repeatedly mass produced and delivered in an off-the-shelf manner, significantly reducing the cost of, and time to, patient treatment.

Fate Therapeutics says it has built a dominant intellectual property position broadly covering iPSC technology and iPSC-derived cell products. Its proprietary portfolio includes compositions and methods for generating iPSCs, including engineering their biological properties using CRISPR and other nucleases, and for producing genetically edited cells of the hematopoietic lineage, including natural killer cells and T cells, from iPSCs. Fate Therapeutics’ iPSC product platform is supported by over 100 issued patents and 100 pending patent applications.

"Pooled CRISPR/Cas9 knockout screens have rapidly become an important tool in novel drug target identification and validation. Horizon continues to innovate in this important area, having launched our CRISPR interference and CRISPR activation screening service in 2017, and through the development of RNAseq-linked CRISPR screening," says Terry Pizzie, CEO of Horizon Discovery.

Horizon’s pooled format screens offer researchers access to highly robust whole-genome level analyses said to yield outstanding data quality. While this approach has proven a potent research tool, it is currently challenging to adequately multiplex the analysis from these screens to evaluate complex biological phenomena. Coupling pooled screening to single-cell RNAseq allows the opportunity to address the impact of CRISPR-based gene modification on a global transcriptomic level, at single-cell resolution. This is intended to enable customers to address critical gaps in target identification and validation as they work to develop novel and more effective drug therapies.

"Pooled CRISPR/Cas9 knockout screens have rapidly become an important tool in novel drug target identification and validation. Horizon continues to innovate in this important area, having launched our CRISPR interference and CRISPR activation (CRISPRa) screening service in 2017, and through the development of RNAseq-linked CRISPR screening," commented Terry Pizzie, CEO of Horizon Discovery. "The co-development of this tool with a major pharma partner provides a substantive advance to Horizon’s already world-leading screening capabilities, offering our customers cutting-edge solutions not available elsewhere."
The hopeful destruction of diabetes

Also in September, Zug, Switzerland-based CRISPR Therapeutics and San Diego-based ViaCyte announced their collaboration focused on the discovery, development and commercialization of gene-edited allogeneic stem cell therapies for the treatment of diabetes. Besides of clinical data with islet transplants indicate that beta cell replacement approaches may offer curative benefit to patients with insulin-requiring diabetes. ViaCyte has pioneered the approach of generating pancreatic-lineage cells from stem cells and delivering them safely and efficiently to patients.

PEC-Direct, ViaCyte’s lead product candidate currently being evaluated in the clinic, uses a non-immunoprotective delivery device that permits direct vascularization of the cell therapy. This approach has the potential to deliver durable benefit, but because the patient’s immune system will identify these cells as foreign, PEC-Direct will require long-term immunosuppression to avoid rejection. As a result, PEC-Direct is being developed as a therapy for a subset of patients with type 1 diabetes at high risk for acute complications.

CRISPR gene editing offers the potential to protect the transplanted cells from the patient’s immune system by ex-vivo editing of immune-modulatory genes within the stem cell line used to produce the pancreatic-lineage cells. The speed, specificity and multiplexing efficiency of the CRISPR system are said to make it ideally suited to this task. CRISPR Therapeutics is pursuing a similar approach for its allogeneic CAR-T programs, and has established significant expertise in immune-evasive gene editing. The combination of ViaCyte’s stem cell capabilities and CRISPR’s gene editing capabilities has the potential to enable a beta-cell replacement product that may deliver durable benefit to patients without triggering an immune reaction.

“We believe the combination of regenerative medicine and gene editing has the potential to offer durable, curative therapies to patients in many different diseases, including common chronic disorders like insulin-requiring diabetes. ViaCyte is a pioneer in the regenerative medicine field, and has built a compelling clinical program, robust manufacturing capabilities and assembled a strong intellectual property position. Partnering with ViaCyte will allow us to accelerate our efforts in regenerative medicine, an area that we believe will provide a variety of longer-term opportunities for our company,” noted Dr. Samarth Kulkarni, CEO of CRISPR Therapeutics.

Under the terms of the agreement, CRISPR Therapeutics and ViaCyte will jointly develop an immune-evasive stem cell line as a first step on the path to an allogeneic stem-cell derived product. Upon successful completion of these studies and identification of a product candidate, the parties will both assume responsibility for further development and commercialization worldwide. Upon execution of the agreement, ViaCyte will receive $15 million from CRISPR Therapeutics, which at CRISPR Therapeutics’ election may be paid in either cash or CRISPR Therapeutics stock. ViaCyte also has the option, under certain circumstances, to receive an additional $10 million from CRISPR Therapeutics in the form of a convertible promissory note.

“Creating an immune-evasive gene-edited version of our technology would enable us to address a larger patient population than we could with a product requiring immunosuppression.”

Dr. Paul Laikind, CEO and president of ViaCyte

CRISPR

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There are many access points for news and knowledge of the world of oncology therapeutics R&D and diagnostics, but in your multitude of choices, don’t overlook DDNews’ Cancer Research News site.

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DEALS
CONTINUED FROM PAGE 37

immunosuppression. CRISPR Therapeutics is the ideal partner for this program, given their leading gene-editing technology and expertise and focus on immune-evaive edit- ing. We are thrilled to have the opportunity to partner with CRISPR Therapeutics on what we believe could be a transformational therapy for patients with insulin-requiring diabetes,” said Dr. Paul Laikind, CEO and president of Velos. “We also believe that this approach may have many other appli- cations which we and CRISPR Therapeutics may explore in the future.”

Making mammalian cell lines

In other licensing news, Oxford Genetics dis- closed back in August that they have secured a multimillion-pound contract with a leading global ecommerce provider of reagents and tools to the research and clinical community. As part of the agreement, Oxford Genetics will leverage its high-throughput automated platform to expand its market in Europe and Asia and continue extending its full stack genome engineering platform to enable access to new capabilities for scientists.

“The precision of genome editing gives it the potential to develop an entirely new class of therapies for human disease. The head- genomic engineering platform for CRISPR modification of mammalian cell lines. Headquartered in Oxford, U.K., Oxford Genetics is a synthetic biology company dedi- cated to developing and delivering technolo- gies and services to its customers that will help to change the gene-editing industry. The company says its use of automation allows it to develop new and innovative solutions, the latest of which is the mammalian CRISPR cell line engineering platform.”

“This contract highlights Oxford Genet- ics’ commitment to providing the highest- quality cell line engineering services to its global customer base and continuing to add value to their operations,” said Ryan Cawood, CEO of Oxford Genetics. “We have moved away from manual processing, which is the norm in this market, in favor of automated, scalable platforms. This approach means we are well positioned to deliver the large num- ber of custom-engineered cell lines per year that the global market is forecast to need.”

Ryan Cawood, CEO of Oxford Genetics

Inscripta is building the tools to take on the next frontier of gene-editing discoveries. The addition of the Solana team brings world-class scientific product development, manufacturing and operations experience to further enable Inscripta to provide the best gene-editing tools to both commercial and academic researchers.”

Kevin Ness, CEO of Inscripta

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Kevin Ness, CEO of Inscripta

“I am thrilled to welcome Tom Ross to our team and make it more accessible for both commercial and academic researchers. The addition of the Solana Biosciences team brings world-class scientific product development, manufacturing and operations experience to Inscripta, helping the company grow, diversify and scale its operations to meet the rapidly advancing needs of the gene-editing industry,” enthused John Stuelpnagel, chair- man of Inscripta’s board of directors, as well as co-founder and first CEO of Illumina. “Together, our team will design, build and commercialize a new suite of tools that will revolutionize life sciences.”

Following the acquisition, Rosso will become vice president of operations at Inscripta and lead the process development, technology transfer, manufacturing and operations teams at the company. In addi- tion, Inscripta will expand operations and obtain a new office in the life-sciences hub of San Diego.

“From my days at Illumina, I know the people behind Solana, and I can say that they will bring unparalleled expertise and experi- ence to Inscripta, helping the company grow, diversify and scale its operations to meet the rapidly advancing needs of the gene-editing industry,” enthused John Stuelpnagel, chair- man of Inscripta’s board of directors, as well as co-founder and first CEO of Illumina. “With the addition of Solana’s talent and capabilities, I am confident that Inscripta will fundamentally transform genome writing, just as Illumina did for genome reading.”
EPO grants ToolGen a patent on Cas9 editing system

SEOUl, South Korea— ToolGen publicized in July that the European Patent Office (EPO) has issued a decision to grant ToolGen a European patent covering a CRISPR/Cas9 genome-editing system adapted for mammalian cells.

Jongmoon Kim, CEO of ToolGen, noted, “We are committed to developing transformative therapeutics and agricultural products using our CRISPR/Cas9 genome-editing system. This patent grant from the EPO begins to lay the groundwork for our intellectual property in Europe and further validates our research efforts.”

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Jongmoon Kim, CEO of ToolGen

Genetics Research granted patent for nucleic acid enrichment method

WAKEFIELD, Mass.—Genetics Research announced in early October that the U.S. Patent and Trademark Office (USPTO) has granted the company U.S. Patent No. 10,081,829, entitled “Detection of targeted sequence regions.”

The patent covers a novel method for enriching sequence specific nucleic acids called Negative Enrichment, in which Cas endonuclease complexes are used to protect targeted sequences of interest in the presence of exonucleases. The exonucleases substantially degrade all of the nucleic acid in a sample except for the nucleic acid of interest, leaving the nucleic acid of interest isolated and amenable to analysis.

Tony Shuber, president and chief operating officer of Genetics Research, said: “Our Negative Enrichment platform is agnostic to the size of the targeted sequence of interest, and our research team has demonstrated the ability to apply our Cas9-associated Negative Enrichment platform to multiple, sequence-specific applications.”

Tony Shuber, president and chief operating officer of Genetics Research

CORALVILLE, Iowa— In a study published in Nature Medicine back in August, researchers at Integrated DNA Technologies (IDT) and the laboratory of Dr. Matthew Porteus at Stanford University described a novel Cas9 mutant that shows improved specificity and maintains high activity when used in the medically relevant ribonucleoprotein (RNP) format. Potential for medical use of the new mutant enzyme was demonstrated in human hematopoietic stem and progenitor cells (HSPCs), where it was able to correct the mutation in the beta-hemoglobin gene responsible for sickle cell disease.

Several groups have previously described Cas9 mutants with improved specificity; however, all show significantly reduced activity when used in the clinically relevant RNP format. These previous mutants were developed using intelligent design based on known protein crystal structures. IDT scientists used an unbiased method to screen approximately 250,000 random Cas9 mutants, in order to identify those rare mutants that improved specificity without compromising activity.

After several rounds of selection a single mutant emerged: Alt-R HiFi Cas9 nuclease, which provides the desired high on-target, low off-target characteristics. In the published study, a collaborative team from IDT and Stanford demonstrated the robust on-target editing and minimal off-target cleavage achieved by HiFi Cas9 in several therapeutically relevant loci in hard-to-edit HSPCs. They also showed HiFi Cas9-mediated correction of the sickle cell disease-causing p.E6V mutation in patient-derived HSPCs.

Previous attempts at improving Cas9 specificity characterized the mutants using plasmid-based methods that result in sustained overexpression of the Cas9 protein, which increases off-target activity and is not ideal for medical applications. This sustained overexpression, however, rescued function of the mutants that otherwise showed low activity when used in the more transient RNP format,” said Dr. Mark Behlke, chief scientific officer at IDT and a co-author of the study. “We specifically performed a broad screen to identify a mutant that performs well when used at the lower protein levels achieved with RNP delivery, maximizing safety and further reducing unwanted side effects. Prof. Porteus demonstrated utility using the new system to correct the SCD mutation in normal human blood-forming stem cells while minimizing known off-target activity. We anticipate significant interest in use of the new Cas9 mutant in translational medical applications.”

The novel HiFi Cas9 nuclease is now commercially available as Alt-R HiFi Cas9 Nuclease V3.
CrownBio expands model options in cancer and more
Company completes validation of prostate cancer PDX model and forms alliance with Shanghai Model Organisms Center

BY JEFFREY BOLEY
SAN DIEGO—Late September saw Crown Bioscience, a global drug discovery and development services company providing translational platforms to advance oncology, inflammation, cardiovascular and metabolic disease research, announce the addition of unique, well-characterized, fully annotated patient-derived xenograft (PDX) models of prostate cancer.

CrownBio notes that prostate cancer is the second most common cancer in males, impacting more than one million new patients worldwide each year, yet the disease has long been under-represented at the preclinical modeling stage of drug development. This, the company says, is because of the difficulty in establishing PDX models.

PDX are the most transplantable preclinical models currently available, directly derived from patient tissue and reflecting the variability and heterogeneity seen in patient populations, the company explains, and they also represent the tumor microenvironment more accurately than in-vitro options, particularly when transplanted orthotopically. Therefore they are the model of choice for preclinical drug discovery and development, and CrownBio’s goal is to “recapitulate the diversity and complexity of human cancer biology in the laboratory.”

“The biopharmaceutical research community has been lacking in well-characterized prostate cancer PDX models. They are extremely difficult to generate and grow in...”

CROWN CONTINUED ON PAGE 41

CMOs to benefit from double-digit approvals for ADCs

CPhI Annual Report predicts that therapeutic ADC market will reach $4 billion by 2023

BY DDNEWS STAFF

MADRID--The global antibody-drug conjugate (ADC) therapies market is expected to grow to $4 billion by 2023, with double-digit approvals within three years, according to a new analysis in the CPhI Annual Report. The complete findings of the report were released live at the CPhI Worldwide conference held in Spain in October.

CPhI Annual Report expert Vivek Sharma, the CEO of Piramal Pharma Solutions, expects the global market for ADCs to grow at around a 19 percent compound annual growth rate between 2017 and 2030 and reach the estimated value of $4 billion in the next five years, with 12 drugs that are either approved or in late stages of clinical development catalyzing that growth.

“The last few years have seen a progressive evolution of targets from first- to second- and third-generation antibody-drug conjugates, which is now accelerating growth as new compounds are more targeted, more drugable and potentially have a better chance for approval,” Sharma said.

The understanding of site-specificity and homogenously conjugated ADCs has accelerated the U.S. Food and Drug Administration approval rate and has led to a dramatic increase in the number of clinical trials for ADCs, especially in solid tumors. In total, there are now 600 clinical trials being conducted worldwide on ADCs, with 202 ADCs entering clinical trials—out of which 116 are actively progressing, according to CPhI. Most encouragingly, there has been an increase of 30 percent in the last 12 months, with 23 new ADCs entering clinical trials.

The report outlines that contract manufacturing organizations (CMOs) and contract development and manufacturing organizations (CDMOs) are particularly well set up to capitalize on this growing therapeutic product class, and may even lead to new business models such as co-development partnerships, particularly among small and medium-sized biotechs.

Due to technical challenges associated with ADC manufacturing and the substantial investment involved on safety and hazardous material equipment, Vivek estimates that around 70 percent of ADC manufacturing is outsourced to CMOs. This is expected to rise, particularly for horizontally integrated CDMOs, along with co-development business models, driven by biotechs and smaller companies that need specialist development expertise and facilities.

The full findings of the CPhI Annual Report are available for free at www.cphi.com/europe/cphi-annual-report

EDITCONNECT: E111825

Global CRO signs agreement with OmniComm Systems
Seven-year TrialOne agreement expands commitment to supporting early-phase studies

BY DDNEWS STAFF
FORT LAUDERDALE, Fla.—A global provider of drug development and commercialization solutions and services has signed a new agreement extending its relationship with OmniComm Systems Inc., a provider of clinical data management technology, for another seven years. Under the terms of the agreement, the contract research organization (CRO) will use OmniComm’s TrialOne eClinical solution to automate early-phase studies at one of its U.S.-based clinical research units.

The CRO selected TrialOne, apart...
CROWN CONTINUED FROM PAGE 40

mice due to multiple issues,” said Dr. Henry Li, senior vice president of global scientific research and innovation for Crown Bioscience. “I am very excited to announce the successful validation of models derived from both castration-resistant and hormone-sensitive primary tissue to add to our extensive collection of more than 2,500 PDX models.”

“At CrownBio we have dedicated significant efforts to the development of these models. We will continue to invest in a diverse collection of models that represents patient populations from different backgrounds globally. Due to their unique nature, we anticipate high demand for these clinically relevant models,” commented Dr. Jean-Pierre Wery, CEO of Crown Bioscience.

A little over a month earlier, the company also had model-related news with a broader reach. Specifically, Crown Bioscience reported that it had entered into a strategic alliance with Shanghai Model Organisms Center (SMOC) to exclusively license and commercialize SMOC’s comprehensive collection of genetically engineered models, including proprietary transgenic and reporter models for oncology, cardiovascular and immunology research.

SMOC leverages expertise in several gene-editing technologies to develop conventional knockout (KO), conditional KO, transgenic knock-in and humanized models. These capabilities are now exclusively available to CrownBio’s international clients for custom model generation, breeding, rapid expansion and re-derivation capabilities and more.

“The strategic alliance with SMOC helps CrownBio become a leading global provider of unique GEM [genetically engineered mouse] models, while significantly expanding CrownBio’s collection of tumor homografts and humanized target models,” said Li. “Researchers working with CrownBio will now have access to thousands of knockout, knock-in and transgenic models as well as cutting-edge services for custom model creation, providing a unique portfolio of models for pharmacology and immuno-oncology research.”

“SMOC is excited to expand the use of our comprehensive GEM models outside of China through CrownBio’s global preclinical research engine,” noted Mingjun Wang, CEO of Shanghai Model Organisms. “The strategic alliance will help advance the shared goal of our organizations: to advance novel immuno-therapy targets worldwide.”

EARLY CONTINUED FROM PAGE 40

from its status as the market-leading eSource and site automation system for Phase 1 clinics, because TrialOne enables research organizations to greatly improve the productivity and efficiency of their Phase 1 clinics.

Browser-based, tablet-compatible TrialOne streamlines and automates key processes for early-phase clinics, which drive efficiencies and reduce timelines and costs through faster and more directed volunteer recruitment, easy-to-build schedule-based workflows, real-time bedside data collection, direct data capture from devices, sample processing automation and data processing. The automation reduces workload on clinic staff and improves the clinical trial experience for volunteers.

Each new contract document TrialOne’s position as the market-leading eSource solution for Phase 1 clinics,” said Dr. Kuno van der Post, OmniComm’s chief commercial officer. “We’re excited to continue building our partnership with this leading CRO.”

SPEAKERS:

Teresa K. Woodruff, Ph.D.
The Graduate School at Northwestern University

Eran Segal, Ph.D.
Weizmann Institute of Science

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Phase II SBIR grant awarded to Celldom

Money supports advancing tech to process phenotypic and genotypic cell data at massive scale

BY KRISTEN SMITH

DURHAM, N.C. — Celldom Inc. has received a $1.5-million Phase II Small Business Innovation Research (SBIR) grant from the National Institutes of Health’s National Institute of General Medical Sciences to advance its single-cell analysis technology platform, with a heightened focus on drug-resistant cancer cells. Launched out of Duke University in 2016, Celldom is a seed-stage biotech company working to refine its TrapTx Analyzer System, which is able to process both phenotypic and genotypic cell data at a massive scale with the promise of advancing research, drug discovery and drug development by illuminating diversity in cell populations.

Upon launching, Celldom shared a compelling origin story: “Gordon Moore once said that if the auto industry advanced as rapidly as the semiconductor industry, a Rolls Royce would get half a million miles per gallon, and it would be cheaper to throw it away than to park it. Celldom says that if biology advanced as rapidly as the semiconductor industry, a biopharma company would be able to analyze half a million drugs per year, and it would be cheaper to fund that effort than what it costs annually to run a typical cell biology laboratory.”

Now, two years later, they have received a major investment in their “Rolls Royce,” the TrapTx system. This SBIR grant was preceded by a Phase I grant which allowed them to establish the efficacy of the system — CELLDOM CONTINUED ON PAGE 43

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BRIEFS

Green light for development deal

MICHELIN, Brussels & PLABUS/MINDOR, Germany — Galapagos NV and MorphoSys AG recently announced that, with the expiration of the waiting period under the Hart-Scott-Rodino Act, they had attained U.S. antitrust clearance for their license agreement with Novartis Pharma AG. The deal to develop and commercialize MOR106 was struck on July 19, 2018, and became effective on Sept. 10. In conjunction with this, the €35 million upfront payment by Novartis is now payable. Per the agreement, the companies will broaden the current development plan for MOR106 in atopic dermatitis, and Novartis will hold all commercialization rights for any products resulting from the deal. In addition, Novartis will be responsible for all future research, development, manufacturing and commercialization costs for MOR106. MorphoSys and Galapagos will conduct additional trials to support the compound’s advancement in atopic dermatitis.

Provectus secures new patent

KNOXVILLE, Tenn. — The U.S. Patent and Trademark Office has allowed Provectus’ patent application for the use of adoptive cell transfer of PV-10-induced T cells for treating solid tumor cancers, the company announced recently. Under the patent’s treatment concept, PV-10 is injected into solid tumors, and then T cells trained through PV-10 oncolytic immunotherapy to target treated tumors are harvested, banked and amplified. These amplified T cells can then be administered via adoptive cell transfer. The patent covers such treatment for either the original patient or other immunologically suitable patients. PV-10, an investigational drug for treating adult/pediatric solid tumor cancers, is the first small-molecule oncolytic immunotherapy. PV-10 is administered through intraskeletal injection into superficial or visceral tumors to trigger immunogenic cell death, and is being evaluated in multiple cancer types.

ON THE CUTTING EDGE

A look at some recent M&A and licensing deals in the pharma and biotech world

BY JEFFREY BOULEY

ACQUISITION is a big part of any business in so many different ways, whether acquiring permission to use intellectual property, gaining access to new markets, absorbing entire enterprises or more—and so we look at several different activities recently, from mergers and acquisitions (M&As) to licensing deals. Let’s start with news that Santa Clara, Calif.-based Agilent Technologies Inc. has signed a definitive agreement to acquire privately owned ACEA Biosciences Inc., a developer of cutting-edge cell analysis instruments for life-sciences research and clinical diagnostics, for $250 million in cash.

“Expanding our cell analysis footprint is a key strategic growth initiative,” said Jacob Thaysen, president of Agilent’s Life Sciences and Applied Markets Group. “Innovative
“Our system has great potential to rapidly test for drug-resistant cells and provide insights towards developing therapeutics that target resistance mechanisms.”

Dr. Kris Wood, co-founder of Celldom

“...reportedly proving that the platform can efficiently organize tens of thousands of single cells on a standard cell culture plate-sized microfluidic chip, and then track the growth rates of single cell clones over time. According to Dr. Zachary Forbes, Celldom’s co-founder, president and CEO, Phase I allowed them to prove that the methodology—relying on hydrodynamic methods and optimized chip designs—was effective and worth further investment. In Phase I of this SBIR grant, we established proof of principle that Celldom’s microfluidic chips and hydrodynamic trapping workflow are capable of organizing an array of single cells at high density (>100,000 single cells can be organized in a footprint the size of a standard cell culture plate) and with high efficiency (~90% of the trap sites contain a single cell),” asserts Forbes. “We have successfully formed single-cell arrays from a variety of cell lines, including suspension cancer cells such as acute myeloid leukemia (AML) cells (MOLM-11) and a chronic myeloid leukemia (CML) cell line (K-562), and adherent cells, such as non-small cell lung cancer (PC-9), breast cancer (MDA-MB-231) and melanoma cell lines (A375). We further showed the ability to transfer the trapped cells into environment which allow them to proliferate for seven days or more. Finally, we demonstrated the ability to measure drug responses on chip that are comparable to results obtained in standard bulk cell culture conditions.”

Receipt of the Phase II grant will allow Celldom to invest in the technology and make it available through contract research services starting in 2019. They have made several hires in the area of molecular biology, biochemistry and bioinformatics, and doubled their footprint at Biobacs NC in Durham’s Research Triangle.

According to Forbes, Phase II has huge potential beyond the NIH project. “Rather than thinking about our product development in terms of the NIH nomenclature, in parallel with our Phase II grant we are moving forward with the integration of our private beta systems and all validated workflow steps into a benchtop instrument with beautiful protocols for cancer drug resistance assays,” he said.

As their usable datasets continue to grow, Celldom expects to increase their protocols in oncology while expanding into immunology and stem cell biology.

“Cancer patients often relapse because their tumors contain drug-resistant cells, which though initially present at small fractions, become enriched during treatment to yield incurable tumors. Traditional approaches to identify, isolate and then examine drug-resistant cells can require months of labor-intensive work, which is often prohibitive for the early stages of drug candidate identification,” said Dr. Kris Wood, Celldom co-founder and an assistant professor of cancer biology at Duke University. “Our system has great potential to rapidly test for drug-resistant cells and provide insights towards developing therapeutics that target resistance mechanisms. Celldom has created an open platform for innovation across a myriad of cell types and applications where rare events in biology require investigation.”

EDITCONNECT: E111827

Stream Bio introduces biomaging probes

STOCKTON-ON-TEES, U.K.—In September, Stream Bio launched its "transformative Conjugated Polymer Nanoparticle (CPN) products with life-sciences distributor 2BScientific. Stream Bio’s non-toxic molecular bioimaging probes, known as CPNs, reportedly provide immense photostability and sensitivity (brightness) with a highly specific target- and magnetic cell purification capability, all while requiring no change to existing lab protocols.

The CPN products can be used in molecular and R&D applications such as flow cytometry, ELISA, FISH, western blotting, FRET, IHS and lateral flow assays. Stream’s CPNs can be purchased in four emission wavelengths from 425 nm to 680 nm, covering colors blue, green, yellow and red. Although Stream’s CPN products are initially aimed at in-vitro R&D, it is hoped that the roll-out of the technology will also positively impact in-vivo R&D, diagnostics and therapeutics in the future.

“We are very excited for our first launch and look forward to extending this into a number of other EU countries in the near future, and ultimately worldwide. We are planning on a rapid expansion of the range over the coming 12 months, extending their utility into a number of new applications and widening their use in our key areas,” noted Steve Self, commercial director at Stream Bio.

Eppendorf SmartExtender brings versatility

HAMBURG, Germany—The Eppendorf ThermoMixer series is an established series globally for the heating, cooling and mixing of samples in the lab. All common vessels can be handled by specialized SmartBlocks on top of the mixer. Now the new Eppendorf SmartExtender, released in September, offers a comfortable incubation tool which can easily be used as an add-on to existing mixers and related SmartBlocks.

Up to a dozen 1.5 mL vessels can be incubated in parallel, and the temperature control for heating is independent from the SmartBlock in use. A second temperature within the same instrument saves time, especially when performing a multi-step workflow like enzymatic reactions or needing a standard incubation temperature in parallel to individual workflows. By taking advantage of the ThermoTop power support connectors, every existing Eppendorf ThermoMixer C, Fx or ThermoStat C can be used with the SmartExtender.

EDITCONNECT: E111823

CAMBRIDGE, U.K. & ENSCHEDE, Netherlands—Evonetix and LionX International announced in early October a collaboration to scale up production of prototype micro-electromechanical systems (MEMs) for DNA synthesis. LionX International plans to use electromechanical systems (MEMs) for DNA synthesis. Evonetix and LioniX International—Evonetix thermally addressable silicon array

For more information, visit www.DDN-News.com
approaches to cell analysis are driving market demand and leading to a better understanding of disease and the discovery of potential therapeutics.”

Since its inception in 2002, ACEA has launched two groundbreaking, highly differentiated platforms. Agilent says, and the company reportedly has been revolutionizing the field of flow cytometry with its high-performance, customizable line of NovoCyte benchtop flow cytometers. ACEA’s xCELLigence technologies, for example, enable label-free, real-time monitoring of cell growth, cell function and cellular responses to a variety of treatments, providing scientists information-rich cellular assays. ACEA is headquartered in San Diego and has a large manufacturing and R&D footprint in Hangzhou, China.

“ACEA represents a unique opportunity for Agilent to expand its team and broaden its portfolio with highly complementary technology, increasing the relevance and impact we can have with our customers in the cell analysis space,” said Todd Christian, vice president and general manager of Agilent’s Cell Analysis Division. “We share the same passion around the need for and innovation of live-cell kinetic and label-free approaches to cell analysis extending beyond traditional end point measurements. Together, we will be able to offer a more comprehensive and compelling product portfolio to our collective customers.”

Supernus to acquire Biscayne Neurotherapeutics

ROCKVILLE, Md.—Mid-September saw Supernus Pharmaceuticals Inc., a pharmaceutical company focused on developing and commercializing products for the treatment of central nervous system (CNS) disorders, announce that it had entered into an M&A agreement for Biscayne Neurotherapeutics, a privately held company developing a novel treatment for epilepsy.

“I am confident that we will be able to obtain worldwide rights (excluding certain markets in Asia where rights have been out-licensed) to Biscayne’s product candidate in Phase 1 clinical development, which has received an Orphan Drug designation from the U.S. Food and Drug Administration for the treatment of Dravet syndrome, a severe form of childhood epilepsy. Supernus will also obtain rights to all the product candidate’s underlying and related intellectual property (IP).”

Transaction terms included an upfront payment of $7 million, payable by Supernus to the current Biscayne security holders, as well as $73 million contingent on achieving certain development milestones and up to $5 million contingent upon achieving certain sales milestones. Supernus will pay a low single-digit royalty on net sales to Biscayne and any applicable royalties to third parties for the use of in-licensed IP.

“The development program, which will be referred to as SPN-817, will utilize a novel synthetic form of huperzine A, a potent acetylcholinesterase inhibitor with pharmaceutical activities in CNS conditions such as epilepsy. Development of SPN-817 will initially focus on the drug’s anticonvulsant activity, which has been demonstrated in preclinical models for partial seizures and Dravet syndrome.

Dr. Stephen Collins, president and CEO of Biscayne, will be retained on a consulting basis to assist with the transition and potentially the future development of SPN-817. He is described as a leader in the field of Dravet syndrome research. Biscayne said of the M&A deal that: “Supernus, with its strong presence in epilepsy and its proven track record in developing and commercializing a number of successful products, represents an ideal partner for us. Huperzine A has a novel mechanism of action that represents a new approach for the treatment of epilepsy. We look forward to working with Supernus and progressing SPN-817 in the clinic, and eventually to its availability to patients.”

VistaGen acquires license for Phase 3-ready CNS drug candidate

SOUTH SAN FRANCISCO & MOUNTAIN VIEW, Calif.—VistaGen Therapeutics Inc., a clinical-stage biopharmaceutical company focused on developing new generation medicines for CNS diseases and disorders with high unmet need, and Pherin Pharmaceuticals Inc., a biopharmaceutical company focused on development of novel treatments for neuropsychiatric and neuroendocrine conditions, announced in September the signing of a license agreement granting VistaGen exclusive worldwide rights to develop and commercialize PH549, a Phase 3-ready drug candidate for as-needed (PRN) treatment of social anxiety disorder (SAD).”

“SAD affects nearly 15 million Americans. Currently, there is no FDA-approved treatment for this debilitating condition. PH549 is rapidly acting, well-tolerated and has the potential to provide meaningful relief for individuals suffering from social anxiety disorder,” said Shawn Singh, CEO of VistaGen. “PH549 clinical data are compelling and support its potential to be a first-in-class, rapid-acting, self-administered, PRN treatment alternative—without sedation, risk of addiction or other safety concerns—for millions affected by SAD in the U.S. and who may be candidates for treatment especially if not only expands and diversifies our CNS pipeline to include SAD, but also firmly complements our patent-protected, neuro-psychiatry focus on MDD with AV-101 in our ongoing Phase 2 ELEVATE Study.”

Biohaven acquires option to biologic agent for inflammatory and autoimmune diseases

NEW HAVEN, Conn.—Biohaven Pharmaceutical Holding Co. Ltd. recently noted that it had signed an exclusive worldwide option and license agreement with the University of Connecticut for the development and commercialization rights to UCMT, a therapeutic antibody targeting extracellular metallothionein (MT). Extracellular MT has been implicated in the pathogenesis of autoimmune and inflammatory diseases. Under this agreement, Biohaven has the option to acquire an exclusive, worldwide license to UCMT and its underlying patents to develop and commercialize the agent throughout the world in all human indications.

The antibody was discovered in the laboratory of Prof. Michael Lynes, head of the Department of Molecular and Cell Biology at the University of Connecticut Storrs and a leader in the study of metallothioneins and their role in disease. Biohaven and the University of Connecticut also signed a sponsored research collaboration agreement to support the ongoing exploration of the role of MT in human disease.

MTs are a family of low molecular weight, cysteine-rich, metal-binding proteins that have a wide range of functions in cellular homeostasis and immunity. MT has traditionally been considered to be an intracellular protein that can be found in both the cytoplasm and nucleus. However, it can also be found in extracellular spaces, particularly in disease states involving chronic cellular stress where intracellular MT production is upregulated by inflammatory cytokines, and extracellular MT acts as a danger sig- nal, attracting leukocytes and modulating the immune response. In preclinical studies, UCMT has been observed to block this extracellular pool of MT and the resulting MT-mediated inflammation and immunomodulation. •

EDITCONNECT: E111828

For more information, visit www.DDN-News.com
HAMBURG, Germany—With October came news that German scientist Dr. Johannes Kohl had won the 2018 DuPont & Science Prize for Neurobiology for his work on neural mechanisms underlying parental care—research carried out in the laboratory of Catherine Dulac at Harvard University.

Specifically, his work has revealed how a small population of genetically defined neurons controls the motor, hormonal and social aspects of parental behavior in male and female mice. Previous work had implicated specific neurons in parenting located in the medial preoptic area (MPOA) of the hypothalamus (a brain area that shares common features with other vertebrates). However, it remained unclear how a small group of neurons could control such a complex social behavior.

First, using anatomical techniques, Kohl revealed that these neurons form a hub in a complex, brain-wide parent-oriented network. Subsequently, he used imaging approaches to visualize the activity of these MPDA neurons during parenting and manipulated their function in behaving animals. Together, these experiments revealed that MPDA neurons form subpopulations, each controlling different aspects of parenting.

This discovery, hyper-specific though it may seem at first blush, potentially provides a new model for how specific components of a social behavior are generated at the neural circuit level, and better understanding of the functional architecture of such circuits will advance scientific understanding of how the brain coordinates complex behaviors. Given how difficult it is to have new changes in conditions like dementia, for example, such understanding could be crucial in future therapeutic research in the neurological realm.

The annual $250,000 DuPont & Science Prize for Neurobiology honors scientists like Kohl for their groundbreaking research, and he becomes the 17th recipient of this international prize, which is awarded jointly by DuPont and the journal Science. Researchers who are 35 years of age or younger and have made outstanding contributions to neurobiological research based on molecular, genetic and cellular biology are invited to apply. The next deadline for applications is June 15, 2019. For more information, visit www.dupont.com/prize.

Allergan study receives migraine research award

DUBLIN—In June, Allergan plc announced that the company’s sponsored CaMEO (Chronic Migraine Epidemiology and Outcomes) study was being recognized with the 2018 Harold G. Wolff Lecture Award. The company has been committed to understanding the natural course of migraine with the acceptance of the manuscript, “Identifying New Subgroups of Migraine Based on Comorbidity and Concomitant Condition Profiles: Results of the Chronic Migraine Epidemiology and Outcomes (CaMEO) Study.”

The American Headache Society (AHS) awards the Harold G. Wolff Lecture Award to the best manuscript on headache, head or face pain, or the nature of pain itself. Allergan has been a leader in chronic migraine research for over 20 years and sponsored CaMEO to support the clinical community by generating data to characterize natural disease course; quantify individual, economic, societal and familial impact of life with migraine (specifically chronic migraine); and provide evidence-based foundation to improve chronic migraine management.

As a leader in migraine treatment, Allergan is committed to understanding the condition’s impact on patients and evaluating both current and pipeline therapies to optimize treatment paradigms,” said David Nicholson, chief research and medical officer of Allergan. “Our data [presented at AHS] underscores our continued goal of addressing the unmet needs of the migraine community.”

This sub-analysis of CaMEO identified natural subgroups (clinically meaningful groups of migraine patients) of those with migraine based on profiles of comorbidities and concomitant conditions. The identification of these subgroups may help inform the classification of migraine, predict progression and identify people who respond to specific treatment classes, rather than using a trial-and-error approach.

“The CaMEO study helps us identify clinically meaningful subgroups of migraine, a first step towards developing a foundation for personalized medicine,” said Dr. Richard B. Lipton, vice chair of neurology and director of the Montefiore Headache Center at the Albert Einstein College of Medicine. “It is a privilege to have CaMEO recognized at this year’s American Headache Society. Furthermore, the data supports the opportunity for new advances in migraine patient care and may lead to meaningful clinical trials.”
**LATE-BREAKING NEWS**

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

‘**BRIGHTE**’ news regarding study of fostemsavir in patients with HIV

LONDON—ViV Healthcare, a global specialist HIV company established in November 2009 by GlaxoSmithKline and Pfizer, announced at the end of October that fostemsavir had successfully bid for over €3.7 million of the €7 million from eight companies to create and exploit model organisms, “Choo added. The elderly population continues to increase.”

**Neurodegeneration is a hallmark of many incurable diseases that are fast becoming major global health problems as the world’s elderly population continues to increase.”**

Dr. Yen Choo, executive chairman of Plasticell, said: “Discovering effective treatments for these conditions will require a deeper understanding of disease mechanisms, as well as more effective drug screening strategies, both of which will benefit from better cellular models of neurodegeneration.”

In addition to Plasticell, the research network also includes the Karolinska Institute, Stockholm, Sweden; the Skövde University, University of Barcelona, Autonomous University of Madrid, Instituto for Bioengineering of Catalonia, Technical University of Dresden and Poitiers SA. ASCTN is funded by the European Union Horizon 2020 Programme under the Marie Skłodowska-Curie Initial Training Network and Grant Agreement No. 813582.

The different participating laboratories specialize in human stem cell manipulation, combinatorial cell culture, directed neuronal and glial differentiation, microfluidics and single-cell analysis, advanced imaging, brain-on-chip and 3D tissue engineering. Moreover, other key specialities include cerebral organoids, ex-vivo gene expression, direct cellular reprogramming, mouse genetic modification, animal models of neurological disease, scaffolding implantation and stem cell transplants into the brain.

**Plasticell receives EU funding to advance neurodegenerative disease research**

**Plasticell will join several other companies to create and exploit advanced cellular models of neurological disorders that are caused by acute or progressive loss of cells in the brain.**

**STEVENVAGE, U.K.—Plasticell Ltd., a developer of stem cell technologies and regenerative medicines, announced in late October that the Advanced Stem Cell Training Network (ASCTN), a European research consortium of which Plasticell is a partner organization, had successfully bid for over £3.7 million in funding from the European Union to create and exploit advanced cellular models of neurological disorders—notably Parkinson’s, Huntington’s and demyelination disease—that are caused by acute or progressive loss of cells in the brain.**

“Neurodegeneration is a hallmark of many incurable diseases that are fast becoming major global health problems as the world’s elderly population continues to increase,” commented Dr. Yen Choo, founder and executive chair of Plasticell.

Fostemsavir is an investigational produg of temsavir, a human immunodeficiency virus type 1 (HIV-1) attachment inhibitor class and is not approved by regulatory authorities anywhere in the world. Fostemsavir is being developed by ViV Healthcare for treatment of HIV-1-infected, heavily treatment-experienced patients in combination with other antiretroviral agents.

Since ViV Healthcare launched in late 2009 with its mission to deliver advances in treatment and care for people living with HIV and for people who are at risk of becoming infected with HIV, Shionogi joined as a shareholder company in October 2012. ViV’s aim is to take a deeper and broader interest in HIV/AIDS than any company has done before and take a new approach to deliver effective and innovative medicines for HIV treatment and prevention, as well as support communities affected by HIV.

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**Late-Breaking News**

**NEWS ITEMS THAT ARRIVED TOWARD THE TAIL END OF THIS ISSUE’S PLANNING AND PRODUCTION PROCESS**
Dr. Mohamed Kabbaj and his lab at Florida State University will examine the safety and efficacy of ketamine treatment in depression and other mental health disorders. Their goal is to find out whether low doses of ketamine are addictive when administered in low doses, how it affects men vs. women and how it interacts with alcohol.

The research is funded by a $2 million grant from the National Institute of Mental Health. Kabbaj’s previous studies, also funded by the NIH, demonstrated sex differences in ketamine’s addictive effects. Men require much lower doses than women to get those effects.

“We’re also going to determine which brain areas are implicated in ketamine’s addictive properties at low and high doses,” he said. “Our work will focus on the nucleus accumbens, an area that is associated with reward and behavioral reinforcement.”

The release of dopamine in this brain area, in response to ketamine administration, leads to activation of two populations of neurons that express either dopamine D1 receptors or dopamine D2 receptors. This project, Kabbaj reported, will try to assess the role of these neuron populations in ketamine’s addictive effects.

Since a large population of depressed patients abuse alcohol, another aim of this study is to examine the interaction between ketamine, depression and alcohol in male and female subjects.

“Hopefully, by the end of these five years, we’ll have more information for psychiatrists to decide whether ketamine can be safely prescribed for suicidal patients and for patients who do not respond to classic antidepressant treat- ment,” said Kabbaj, a professor in the Department of Biomedical Sciences.

Ketamine was developed in the 1960s as an anesthetic to replace PCP, which was giving patients hallucinations and other so-called “disassociative effects.”

In the last decade, psychiatrists discovered that ketamine in low doses also worked remarkably fast to relieve symptoms of depression and reverse thoughts of suicide. “A lot of clinics have popped up around the country treating depression and bipolar disorder with repeated infusions of ketamine,” Kabbaj said. “But no studies have been done to look into the safety of these treatments related to ketamine’s potential addictive and cognitive effects.”

In large doses, ketamine is abused by people seeking a quick high. With that dosage, side effects include addiction. Kabbaj’s goal is to find out whether low doses of ketamine are also addictive and determine the mechanisms of ketamine’s actions at both high and low doses in both sexes.

Exploring low-dose ketamine for depression TALLAHASSEE, Fla.—For some people who get no depression relief from Prozac-type medicines, a fast-acting substitute can be found in a drug called ketamine. But concerns exist as to its safety, and to that end, the National Institutes of Health awarded a Florida State University researcher nearly $2 million to investigate ketamine.

Over the next five years, College of Medicine researcher Dr. Mohamed Kabbaj and his lab will seek answers to safety and also other questions, like whether ketamine is addictive when administered in low doses, whether it affects men and women differently, and how it interacts with alcohol.

“Since a large population of depressed patients abuse alcohol, another aim of this study is to examine the interaction between ketamine, depression and alcohol in male and female subjects.”

And even as there are concerns about mixing alcohol and ketamine, there is also the possibility that some of ketamine’s effects on drinking alcohol might be therapeutic, Kabbaj said, noting: “There are some studies now showing that ketamine can reduce alcohol drinking. Our study will directly test these interactions and examine the potential mechanisms behind them.”

Kabbaj’s previous studies, also funded by the NIH, demonstrated sex differences in ketamine’s antidepressant effects. Women require much lower doses than men to get those effects.

“We’re also going to determine which brain areas are implicated in ketamine’s addictive properties at low and high doses,” he said. “Our work will focus on the nucleus accumbens, an area that is associated with reward and behavioral reinforcement.”

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“Hopefully, by the end of these five years, we’ll have more information for psychiatrists to decide whether ketamine can be safely prescribed for suicidal patients and for patients who do not respond to classic antidepressant treatment,” said Kabbaj, a professor in the Department of Biomedical Sciences.
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David Winpenny, Alzheimer’s Research UK, Cambridge Drug Discovery Institute*

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