ALS hope at last?

Small-molecule targets may prevent ALS

BY KRISTEN SMITH

JUPITER, Fla.—Florida researchers have homed in on a compound believed to arrest the most common known genetic cause of amyotrophic lateral sclerosis (ALS) and related forms of dementia. Dr. Matthew Disney from The Scripps Research Institute, working in collaboration with Dr. Leonard Petrucci of the Mayo Clinic in Jacksonville, Fla., believes they have uncovered a novel small-molecule compound that may well translate into a preventative drug candidate.

“There are zero therapies that address the root cause of these diseases. Zero. Our goal is not to target the symptoms, it is to target the root cause, which [we believe] is in the RNA,” explains Disney. “We are assessing its potential to become a drug to treat both diseases. Hopefully, this will be an accelerant not only for us but for all people in the field working toward a treatment for ALS.”

The scientists had been investigating the cellular mechanisms that cause neurodegeneration in diseases characterized by abnormal protein aggregation, such as Alzheimer’s disease, frontotemporal dementia (FTD) and ALS. It is the death of the nerve connectors between muscles and the brain that leads to ALS symptoms of muscle atrophy, weakness, difficulty swallowing and trouble breathing.

ALS is a progressive neurodegenerative disease that affects nerve cells in the brain and the spinal cord, weakening muscles and impacting physical function. Medication and therapy can slow ALS and reduce discomfort, but there is, as yet, no cure.

In frontotemporal dementia, the toxic protein appears to be a cause of neuron death in parts of the brain that control behavior and personality, the frontal and temporal lobes. Disney’s compound, a small molecule

alternative to animal testing

by ILENE SCHNEIDER

ORLANDO, Fla.—Animal activists decry the use of animals as lab test subjects for obvious reasons. Researchers have another issue: animal tests make therapies look promising in the lab, but often fail when eventually tried in humans.

A collaborative effort of the cosmetic company L’Oreal, biotech firm Hesperos Inc. and the University of Central Florida (UCF) has made progress in reducing the reliance on animal testing in drug and cosmetics development.

“If we can prove that the data from our method are better, we can eventually eliminate animal testing,” said Hesperos chief scientist James J. Hickman, who is a professor at UCF’s NanoScience Technology Center. He estimated that the result could be a $2-billion to $10-billion industry, representing a paradigm shift in toxicity testing.

Replacing animal models as test subjects in drug and cosmetics development is one step closer to reality with the successful testing of multi-organ “human-on-a-chip” models to summarize the 28-day experiments used in animals to evaluate the systemic toxicity of drug and cosmetic

Researchers at MD Anderson Cancer Center (pictured here) and colleagues elsewhere are making progress toward effective treatment for brain cancer, with promising work coming out of studies on immunotherapy for glioblastoma and melanomas that have spread to the brain.

Immunotherapy before surgery?

Trial indicates that the process shows benefit for glioblastoma patients

BY JEFFREY BOULEY

HOUSTON & LOS ANGELES—While glioblastoma is the most common, most aggressive and deadliest form of brain cancer, its primacy hasn’t translated into a great many therapeutic options. Tumor heterogeneity and the challenges of getting drugs past the blood-brain barrier make it difficult to treat glioblastoma, and thus median overall survival for primary glioblastoma is 14.6 months with the standard treatments of surgery, radiation therapy and the chemotherapy temozolomide—falling to 5.5 to 11 months for recurrent glioblastoma.

While immunotherapies such as immune checkpoint inhibitors—and the promising research results around them for some cancers, like leukemia and melanoma—are giving researchers, clinicians and patients increasing hope for effective therapies, this area of study and treatment is still a new one.

A recent clinical trial could be a boost for those hopes. Results from a recent study conducted by researchers at the University of
350 AND COUNTING...
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News of financing rounds for Mogrify, Vyome, Cabaletta, Candel and Attune

BY JEFFREY BOULEY
CAMBRIDGE, U.K.—Some say that money is “the root of all evil,” but mostly likely startup companies and venture capitalists would overwhelmingly disagree. And in that theme, let’s start with the roots of growth and news on Feb. 20 of a $3.7-million seed funding round completion for Cell Mogrify Ltd.

Cell Mogrify’s technology is said to enable the conversion of any mature cell type into any other mature cell type without going through a pluripotent stem cell state or progenitor cell state, with the aim to address “the unmet market need for cell types that exhibit safety, efficacy and scalable manufacturing profiles suitable for development as lifesaving cell therapies.” The company has declared that it plans to “raise a significant Series A round to capture a share of a $30-billion market opportunity”—that market being cell therapy development as lifesaving cell therapies. The company has declared that it plans to “raise a significant Series A round to capture a share of a $30-billion market opportunity”—that market being cell therapy development and manufacturing. Cell Mogrify also considers itself well positioned to directly address growing markets that “are unserved by approved cell therapies, such as cardiac repair and cartilage regeneration end-user markets, estimated to be worth $120 billion and $7 billion by 2022 and 2025, respectively.”

Along with the seed funding news came word of the appointment of Dr. Darrin M. Disley as CEO. Disley is a renowned scientist, entrepreneur, angel investor and enterprise champion who has started, grown or invested in over 40 startup life-sciences, technology and social enterprises, and he served as CEO of Horizon Discovery Group plc for 11 years.

“Direct reprogramming between mature human cell types is a holy grail in regenerative medicine and social enterprises, and he served as CEO of Horizon Discovery Group plc for 11 years. Along with the seed funding round, pictures from the company left to right) are Dr. Darrin M. Disley, CEO; Dr. Julian Gough, chief scientific officer; and Pierre-Louis Joffrin, corporate development associate. From the company left to right) are Dr. Darrin M. Disley, CEO; Dr. Julian Gough, chief scientific officer; and Pierre-Louis Joffrin, corporate development associate.
EYES
CONTINUED FROM PAGE 3
Ophthalmology division at GlobalData. “As A.J. Abramson was expecting to reach blockbuster status, its termination was also a significant blow for Roche.”

Besides these drug-related developments, in June 2018 Novartis announced that it plans to spin off Alcon, its long-struggling eye care unit. As GlobalData noted, this move may have been expected, given that in recent years Novartis has exited various spin-offs, sold its animal health business and dropped its consumer health unit in an effort to focus on its core markets.

Additionally, in September the media circulated rumors that Takeda may shed Shire’s ophthalmology business as their mega-merger is completed in an effort to cut debts.

Musciaco concludes: “These challenges suggest that the future of this market, including the fact the anatomy of the eye represents a challenge for R&D and ocular drug delivery. As such, the ophthalmology market has typically been associated as a small specialist field. Nevertheless, it is expected to see solid growth going forward.”

Looking at a specific segment of the ophthalmology market, GlobalData also noted in January that development of drugs with novel mechanisms of action (MOAs) is marking “a shift in glaucoma therapeutic strategies.”

As the company notes, no new classes of drugs have been developed for the treatment of glaucoma in the last 20 years, so the focus of pharmaceutical companies has begun to shift towards the development of glaucoma drugs with novel MOAs, and this trend is expected to continue to 2026. The launch of 11 new therapies will drive growth in the glaucoma space, provide more options for patients and stimulate further competition, adds GlobalData.

The glaucoma pipeline features 120 drugs across all stages of development, with more than two-thirds of the pipeline drugs being developed in early stage. Small molecules are the focus of drug developers, as these constitute more than 68 percent of the total glaucoma pipeline drugs. Glaucoma is an established indication, with large numbers of treatments having become available over the years—as a result, the disease is generally associated with low levels of unmet needs. However, there is some unmet need in terms of achieving better patient compliance.

“The importance of a greater compliance in glaucoma is reflected in the late-stage pipeline, which contains several products developed to help meet this unmet need,” said Alessio Brunello, a pharma analyst at GlobalData. “In particular, there are two SR implants, Ocular Therapeutics’ OTX-TP and Allergan’s Bimatoprost SR, which will provide a sustained release of drugs directly into the eye and avoid potential issues of non-compliance associated with topical drugs. These two products, when they will be launched, are expected to have a significant impact on the glaucoma market.”

FINANCE
CONTINUED FROM PAGE 3
AUBURNDALE, Mass.—Jan. 4 saw Candel Therapeutics, a clinical-stage biotechnology company developing novel cancer immunotherapies, announce acceleration of its Phase 3 registration trial under a Special Protocol Assessment for newly diagnosed, localized prostate cancer and a Phase 2 trial for active surveillance, advance its late-stage high-grade glioma program; expand and further advance clinical programs in pancreatic cancer; and advance other solid tumor indications.”

If approved, the company’s GMCi-derived product candidate could become the first therapeutic to treat low- and intermediate-risk prostate cancer. Said Aguilar-Cordova: “We expect that in a few short years, as a result of our efforts and that of our many collaborators, there will be a new standard of care for this dreadful disease that will significantly improve and extend the lives of nearly 200,000 men each year in just the United States.”

Another $23M against hereditary angioedema
NEW YORK—In late January, Attune Pharmaceuticals Inc., a biotechnology company focused on the discovery and development of novel, orally administered, small-molecule therapeutics for the treatment of rare diseases, completed a $23.5-million Series B financing. Proceeds of this round will be used to advance Attune’s pipeline, which includes the ongoing clinical development of ATN-249, a novel orally administered plasma kallikrein inhibitor for the treatment of hereditary angioedema (HAE). HAE is a rare genetic condition that causes episodic, potentially life-threatening swellings that can affect any part of the body.

Dr. Andrew McDonald, CEO of Attune, noted, “This financing brings together a syndicate of investors with deep understanding and long history of supporting companies that develop novel HAE therapeutics. Building upon our recently announced positive Phase 1 data, the Series B enables Attune to rapidly advance our lead clinical program through Phase 2 while also providing capital for our other preclinical discovery programs.”

Eyes and nose for new players
PRINCETON, N.J.—On Jan. 3, Vyome Therapeutics Inc., a specialty pharmaceutical company developing novel medicines for treating skin diseases caused by resistant microbes, announced an out-licensing deal of marketing rights with a large specialty pharmaceutical company developing novel cancer immunotherapy therapeutics, announce the closing of a $28.7-million Series B financing. Proceeds of this round will be used to advance Attune’s pipeline, which includes the ongoing clinical development of ATN-249, a novel orally administered plasma kallikrein inhibitor for the treatment of hereditary angioedema (HAE). HAE is a rare genetic condition that causes episodic, potentially life-threatening swellings that can affect any part of the body.

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*See Application Note 168 for more details.
Copper conflict

Staphylococcus genes offer potential pathways for overcoming antibacterial resistance

BY JIM CIRIGLIANO
NEW BRUNSWICK, N.J.—A research team at Rutgers University discovered a pair of genes present in some dangerous strains of Staphylococcus bacteria that bestow the bacteria with resistance to copper, a frequently used antibacterial agent. The study, published in February, suggests that strains of the bacteria can acquire additional genes that promote antibacterial resistance, and identifies the function and structure of these genes in the hopes of opening new paths for the development of antibacterial drugs.

The antibiotic-resistant bacterium Staphylococcus aureus is one of the leading causes of serious, life-threatening infections in the United States. S. aureus bacteria live on skin and have become a scourge in hospitals and healthcare settings due to their high resistance to copper-based antibiotics. These bacteria include well-known antibiotic-resistant strains such as MRSA and VRSA.

The study aimed to examine why copper resistance of Staphylococcus aureus is so prevalent, as well as how it can lead to the development of new drugs to combat these bacteria. The team found that the copper resistance in these bacteria is due to a gene called copL, which confers resistance to copper in the bacteria. The gene encodes an enzyme that can reduce the toxicity of copper, allowing the bacteria to survive in copper-rich environments.

GWAS and new gene answers

Genomic exploration by Chinese researchers uncovers new information regarding genetic schizophrenia risk

BY KELSEY KAUSTEN
BEIJING—Schizophrenia is a mental disorder characterized by symptoms such as hallucinations or delusions, movement disorders, reduced emotional expression or pleasure, poor executive functioning, or issues with poor memory. According to the National Institute of Mental Health (NIMH), part of the U.S. National Institutes of Health, the condition most often appears between the ages of 16 and 30, though cases in children do occasionally present, and more than 200,000 cases are seen each year in the United States alone.

At present, though there are some answers about the nature of the disease, the pathogenesis of schizophrenia “remains elusive,” according to authors of a recent Nature Communications paper. A team of researchers from the Chinese Academy of Sciences has delved deeper into the genetics of the disease in pursuit of more specific information, and have uncovered related genes and potential targets.

While previous genome-wide association studies (GWAS) have pinpointed more than 140 independent risk loci related to schizophrenia, the authors note in their paper that “how the risk variants in the reported loci confer schizophrenia susceptibility remains largely unknown.” They further explored those risk variants in a paper titled “Functional genomics reveal gene regulatory mechanisms underlying schizophrenia risk.” The research team used functional genomics—including 30 chromatin immunoprecipitation sequencing (ChiP-Seq) experiments—to uncover new gene answers.
COPPER
CONTINUED FROM PAGE 6

is so toxic to Staphylococcus and how some strains achieve resistance. Previous studies have described two genes that appeared to play a role in copper detoxification.

“We created a mutant S. aureus strain lacking the described copper detoxification genes (CopAZ),” says Jeffrey M. Boyd, senior author of the study and associate professor in the Department of Biochemistry and Microbiology in Rutgers’ School of Environmental and Biological Sciences. “Interestingly, this mutant strain was as resistant to copper as the parent strain. This led us to hypothesize that our strain of S. aureus has an alternate copper detoxification mechanism. Using bioinformatic analyses, we identified a gene encoding a putative mechanism. Using bioinformatic analyses, we identified a gene encoding a putative

COPPER-RESISTANT STAPHYLOCOCCUS AUREUS...
STEM CELLS AND SCREENING

Ncardia seeks to bring human disease biology earlier into drug discovery and development

BY DDNEWS STAFF

LEIDEN, the Netherlands—Early February saw Ncardia, a provider of human induced pluripotent stem cell (iPSC)-derived cell-based assays and services for drug discovery and development, announce the launch of their DiscoverHIT drug screening platform. The new service enables researchers to access human disease-relevant biology earlier in the drug discovery process with the goal of bringing better medicines to patients faster.

The DiscoverHIT Platform is a phenotypic drug screening platform composed of four integrated modules:

- Disease models: Genetic and induced human iPSC-derived cardiac and neural disease models
- Large-scale manufacturing: Controlled bioreactor-based manufacturing to enable batch sizes compatible with high-throughput screening (HTS)
- Customized assay development: Generation and validation of disease-relevant assays with clinically relevant readouts
- High-throughput screening: Robust HTS using qualified disease assays in combination with high content data acquisition and analysis.

“Ncardia enables discovery with efficacy in mind from the start. To realize this, drug developers need validated human iPSC products at scale, disease models, the right assay systems and high-throughput screening. We’ve brought these components together in the DiscoverHIT platform,” said Stefan Braam, CEO of Ncardia.

In addition to the four core modules of DiscoverHIT, Ncardia also offers access to a comprehensive compound library, scientific consultation and the company’s newly founded training center, Ncardia Academy.

“Ncardia enables discovery with efficacy in mind from the start. To realize this, drug developers need validated human iPSC products at scale, disease models, the right assay systems and high-throughput screening. We’ve brought these components together in the DiscoverHIT platform.”

Stefan Braam, CEO of Ncardia

GWAS CONTINUED FROM PAGE 6

Target genes of the TF binding–disrupting SNPs provide further support for the neurodevelopmental hypothesis of schizophrenia.” CTCF binding was found to be “frequently disrupted by the schizophrenia risk SNPs,” and CTCF has been implicated in previous schizophrenia genetic studies, the authors add, which could represent another target.

This isn’t the only recent news in schizophrenia. The Academy shared news in mid-January announcing that a research group from the Institute of Science and Technology for Brain-Inspired Intelligence, which is affiliated to Fudan University, had found that the volume of putamen (a structure found in the subcortical brain region) in adolescents is indicative of a higher chance of developing schizophrenia after adulthood. Their results came from a computational analysis of more than 10,000 data samples of imaging genetics from more than 20 institutions, as noted in a press release, and the sample “was a longitudinally neuroimaging cohort of about 2,000 healthy adolescents,” per the researchers.

Prior to that, scientists from the Chinese Academy of Sciences and Emory identified several “master keys,” which are risk genes found at the center of a network of genes as noted in a press release, and the sample “was a longitudinally neuroimaging cohort of about 2,000 healthy adolescents,” per the researchers.

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CDD

hold the full structure information which can then be converted into an InChI identifier. Similarly, in order for MinChI to gain traction, new data structures and methods are needed to process the information to be converted into MinChI codes, retaining the additional important descriptive details that InChI identifiers intentionally discard.

CDD proposes to develop this data structure—tentatively called “MxiChI” in analogy to Molfile—along with associated conversion routines and a visual editor essential to implement the MinChI standard. Dr. Alex Clark, a CDD scientist, is a member of the IUPAC/MinChI working committee which is encouraging CDD to address this critical prerequisite to adoption of MinChI. CDD has committed to distribute these key infrastructural elements as open formats and open-source software.

The company also recently won another Phase 2 SBIR grant from NIH NCATS, entitled “Novel Deep Learning Strategy to Better Predict Pharmacological Properties of Candidate Drugs and Focus Discovery Efforts.” CDD is planning to develop a novel approach based on deep-learning neural networks to encode molecules into chemically rich vectors. CDD is aiming to first apply this representation to build more powerful computational models that can more accurately predict properties—such as bioactivity, ADME/Tox and pharmacokinetics—across libraries of molecular structures. The ultimate goal with this work is to leverage this representation to generate novel compounds with better combinations of properties.

When building a model to predict a pharmacological property of a series of molecules, computational chemists start by selecting what they believe to be the relevant chemical features, then assemble vectors of molecular descriptors (or fingerprints) that characterize these features in order to represent the molecules and perform a regression analysis over the vectors. This approach reduces dimensional complexity and makes the model tractable, but also throws away much important structural information about the molecules.

In recent years, many groups have tried to work around this limitation by applying deep-learning techniques, but these efforts have only improved the prediction accuracy of computational chemistry models in a handful of cases, where large sets of assay data are available to train the models. CDD’s approach is to apply deep learning to the more focused problem of encoding the RNA features of molecules into chemically rich vectors. The company plans to do this by coupling the encoder to a complementary decoder, creating an autoencoder, then training both neural networks jointly by asking them to try to make the output of the decoder identical to the input to the encoder. Self-training the autoencoder doesn’t require any assay data, but instead relies on feeding it molecular structures (which are conveniently curated in the millions). The chemically rich vector is a narrow layer wedged between the encoder and the decoder to create an information bottleneck, forcing it to become rich in chemical structure information. CDD’s approach is to extract this chemically rich vector and repurpose it as a substitute for conventional molecular descriptors to improve existing predictive models of any type.

The chemically rich vectors will make existing models tractable without sacrificing structural detail. The computationally intense training can be performed once, then applied to diverse problems. CDD says their preliminary tests support the hypothesis that the richer structural information preserved in these novel vectors will significantly enhance the performance and ease of use of predictive regression models.

CDD notes that specific aims for Phase 1 are: to re-implement the chemical autoencoder strategy with a new architecture that accepts a natural representation of the molecular graph as input, and show a substantial improvement compared with their current architecture based on SMILES strings, which follow an obscure grammar; and to exploit the chemically rich vectors to develop ~4 predictive models for diverse pharmacological properties of general interest, and compare the performance of the models with the best-published benchmarks.

CONTINUED FROM PAGE 1

ALS

Speaking of research into combating amyotrophic lateral sclerosis and related forms of dementia, Dr. Matthew Disney of The Scripps Research Institute says, “There are zero therapies that address the root cause of these diseases. Zero. Our goal is not to target the symptoms, it is to target the root cause, which [we believe] is in the RNA.”

Scientists at Scripps Research are investigating the cellular mechanisms that cause neurodegeneration in diseases characterized by abnormal protein aggregation, such as Alzheimer’s disease, frontotemporal dementia and ALS—and their work might be zeroing in on a way to treat ALS.

For Disney and his colleagues, the next steps will be to apply their findings to animal models searching for optimal medicinal chemistry for the best possible therapeutic outcomes. “We have good reason to believe that this can be done,” Disney says. “The question is would potency and selectivity be enough to get to a patient and ‘do no harm.’ We are very optimistic.”
Editor’s focus: Filling the voids

BY JEFFREY BOULEY

THROUGHOUT MY YEARS of writing this editorial column and pepper-
ing my insights and concerns into other pieces in this magazine as well, I have periodically spoken about the lack of investigational drugs for largely unmet conditions—or conditions that we once had a handle on, which are now getting away from us.

Just last year, in October, I talked about schizophrenia and the dearth of material that I see about R&D, much less trials, for therapeutics that would directly and adequately treat the condition. And behold, not long after that we had a “Daily News” article on our website posted by Associate Editor Mel J. Yeates titled “SEP395365 successful against schizophrenia” “talking about a pivotal Phase 2 study that evaluated the efficacy of a drug.”

In creating novel therapeutics in the future or figuring out how to make existing drugs used for schizophrenia work better. And in this issue, beginning on page 6 in our “Discovery” section, an article about schizophrenia-related work from the Chinese Academy of Sciences penned by Managing Editor Kelsey Kaufstein.

Now, I won’t take any mystical credit for “speaking things into action” because I am no wizard or deity, but it is nice to see my concern so quickly followed by signs that things are improving. And to do justice to regroup and see if anything can be salvaged from this massively expensive undertaking. Unfortunately, none of my friends has acted on that having enough potential for return on investment. And yet so many growing problems with antibiotic resistance demand that we get more options—and soon.

There, I see signs of progress and hope a bit more often, and in this issue we have another article in the “Discovery” section talking about research at Rutgers University related to antibiotic resistance, plus clinical trials results for an antibiotic from Paratek Pharmaceuticals called Nuzynary—a drug that the company just announced in October had received FDA approval, making it the first once-daily intravenous and oral antibiotic approved to treat pneumonia and skin infections in nearly 20 years.

And outside of the directly clinical realm, after years of lurking on the sidelines, artificial intelligence (AI) has really been showing its mettle, so much so that we ran a Focus Feature last month on the topic. Even with the increasing attention that AI is getting and the strides it is making, I had worried I might not have enough material—but instead I ended up with so much that we have a sequel to that Focus Feature in this very issue, beginning on page 32.

Here’s to more voices being filled in the life-sciences and pharma/biotech with regard to drug discovery and development. Even if I haven’t complained about them yet.

OUT OF ORDER: KEEP TALKING

BY RANDALL C WILLIS

I AM CONSTANTLY AMAZED at how often my activities align with events in the world around me.

As I share these thoughts with you, Canada is engaged in #BellLetsTalk day, world around me. I think of my many friends who struggle with some form of autoimmune condition—e.g., Crohn’s, rheumatoid arthritis, diabetes, multiple sclerosis—and I recall the pain and disability they regularly face in their lives. Even in treatment that offers relief, my friends cope with the side effects like temperature hyperensitivity, vulnerability to infection and loss of mental acuity.

We’ve talked in our past of our success in transforming some cancers from an acute condition to a chronic one, something patients can learn to live with rather than die from. And yet, I know several people with severe chronic health conditions who have at least once considered whether they wouldn’t be better off dead. Fortunately, none of my friends has acted on that much hope arising from early studies and news reports, only to ride the cycle into despair over yet another failure.

I am also in the earliest stages of research for my Special Report on Immunology and Autoimmunity, which you will find in this issue on page 18. As with any such report, my goal is to examine not only where we are, but to determine where the field is going next, interviewing people whose daily lives revolve around the subject, who hold out hope for the next advance.

But even as I prepare the article, I think of my many friends who struggle with some form of autoimmune condition—e.g., Crohn’s, rheumatoid arthritis, diabetes, multiple sclerosis—and I recall the pain and disability they regularly face in their lives. Even in treatment that offers relief, my friends cope with the side effects like temperature hyper-sensitivity, vulnerability to infection and loss of mental acuity.

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Antibody-based therapeutics have been gaining traction in recent years, but the idea of antibody-drug conjugates, or ADCs, has brought the concept to a new level. In ADCs, an anticancer drug is coupled with an antibody that can target a specific tumor marker. By combining the targeting capabilities of monoclonal antibodies with the tumor-killing power of cytotoxic drugs, the idea behind ADCs is to allow for discrimination between healthy and diseased tissue, something that is lacking in therapeutic options like traditional chemotherapy.

**COMMENTARY: A tale of safety and consistency**

The challenges of bringing ADCs to market

**BY DR. ULRIKE HERBRAND, CHRISTOPHER SUCATO AND ALVARO JORGE AMOR OF CHARLES RIVER LABORATORIES**

For decades, cancer treatment was driven by chemotherapeutic agents that triggered cell death in tumors, but unavoidably imbibed the entire body with a cytotoxic dose of the active compound.

Small-molecule strategies were later joined by monoclonal antibody (mAb) therapeutics, which in theory had more focused targets, but displayed limited efficacy in oncological cases, as measured by only limited tumor cell death.

Antibody-drug conjugates (ADCs), which expropriate tumors and unlock a payload of toxic material, are a way around this. ADCs combine the best of protein- and small molecule-based therapies; antibodies are covalently joined to toxins via a linker in order to act as drone-like weapons against tumors.

ADCs are a booming area of development. The non-profit Antibody Society reported last year that there were 52 clinical trials of ADCs ongoing, many in Phase 2 or Phase 3 trials. The ADC market was valued at $1.3 billion in 2016 and is expected to hit $3.1 billion by 2022, according to the pharmaceutical group biotech firm Charles Johnson, CEO of ADC Bio, compared aggregation to scrambling an egg, by which both processes cause loss of access to the original functional form.

Uncontrolled aggregation can diminish the clinical efficacy in vivo or, in extreme cases, trigger a serious immunogenic response in patients after taking the ADC. Regulatory agencies have recognized the importance of screening for protein aggregation and put pressure on the biotherapeutics industry to find ways that adequately address it. In order to demonstrate clinical safety and efficacy, immunogenicity testing is now a key component of biotherapeutic drug development.

Dynamic light scattering (DLS) is one of the most effective techniques for submicron size analysis of proteins, their aggregates and other nanoparticles. DLS provides rapid measurements of hydrodynamic radius, degree of polydispersity, temperature of aggregation onset and colloidal stability.

Food and Drug Administration (FDA) and European Medicines Agency (EMA) require ADCs to be evaluated with an excipient—often a polymer for size and charge control. A mass balance is also performed to determine the extent of protein aggregation and other degradation.

Protein analytics

One major issue with ADC production is aggregation, which occurs during the purification, processing or storage of the product. Charles Johnson, CEO of ADC Bio, compared aggregation to scrambling an egg, by which both processes cause loss of access to the original functional form.

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ORDER

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COMMENTS

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for this issue, I have initiated research on April’s Special Report on non-small cell lung cancer with a focus on advances in our understanding of and the diagnosis and treatment of depression syndromes, including the role that oncoproteins may play. I know I have come close to losing—and have lost—friends and family to depression. And it might seem that we could never equate the challenges of clinical depression with the suffering of chronic disease or with the anger, frustration and sadness of failed drug development programs, the emotional, psychological and physiological turmoil that comes with each of these, I believe, intimately linked.

Any of these states can lead to feelings of personal insufficiency—e.g., why am I not strong enough?—or solitude—e.g., no one can possibly understand—or fear—e.g., what is wrong with me? And when the stakes are so high, it can seem virtually impossible to simply slough things off and move forward. Sometimes, though, all we have at hand is our ability to talk, to share. And in doing so, hopefully realize that we are not alone in our feelings. And perhaps, in learning of others’ experiences, we can see opportunities that we had not considered before, or together discover new approaches to get through the day, week, month, year.

To the researchers and clinicians, share your experiences and know that even failure comes with learning that brings us closer to solutions, if excruciatingly slowly.

To corporations and investors, see beyond the sometimes painful financial reports and remember that there is a greater purpose to affect change in areas that touch us all.

To patients and families, please know that you have a world of understanding out there, striving to make your lives better. And know that you don’t have to be a passive partner, simply awaiting what you are given, but rather can be a very active participant, opening new avenues of exploration and engagement. You are more than the medical condition.

Start or join a conversation. Share and find support. Keep talking.

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12. Ulrich Herbrand, Ph.D., is a senior scientist, biophysical characterization for Charles River in Erlkraft, Germany. She is an expert in monitoring and optimizing bioscapes for protein therapeutics, specifically monoclonal antibodies.
13. Christopher Susotto, Ph.D., is a senior scientific, biophysical characterization for Charles River in Weburn, Mass. Christopher is the lead scientist for biophysical characterization, with research experience including characterization of protein-protein and protein-nucleic acid interactions by a range of techniques, the evaluation of kinetic interaction constants and protein expression and purification.
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DUAL APPROACH TO PANCREATIC CANCER

Roswell Park researchers publish two studies on progress against the disease

BY KRISTEN SMITH

BUFFALO, N.Y.—Pancreatic cancer is known for a particularly poor prognosis following diagnosis, due to the absence of telltale symptoms when in its early stages and the cancer’s remarkable ability to replicate and metastasize while resisting existing treatment options. There are usually no symptoms in the disease’s early stages, and symptoms that are specific enough to suggest pancreatic cancer typically do not develop until the disease has reached an advanced stage. By the time of diagnosis, pancreatic cancer has often spread to other parts of the body.

Two recently published articles outline promising research emerging from Roswell Park Comprehensive Cancer Center that may help reverse the lethality of pancreatic cancer. Companion articles published in the journals Oncogene and Clinical Cancer Research report on Roswell scientists’ preclinical efforts to apply treatments known to be effective in treating other kinds of solid-tumor cancers.

“Pancreatic adenocarcinoma is a particularly complex cancer with many different genetic subtypes,” says Dr. Agnieszka Witkiewicz of Roswell Park Comprehensive Cancer Center. “Pancreatic cancer has a very poor prognosis, and determining new mechanisms for therapeutic intervention is obviously important.”

“Pancreatic adenocarcinoma is a particularly complex cancer with many different genetic subtypes,” says Dr. Agnieszka Witkiewicz of Roswell Park Comprehensive Cancer Center. “Pancreatic cancer has a very poor prognosis, and determining new mechanisms for therapeutic intervention is obviously important.”

From single-cell to many cells

Researchers use RNA sequencing to investigate spermatogonial stem cells and tackle infertility

BY KELSEY KAUSTINEN

SAN DIEGO—Spermatogenesis, or the production of sperm, is an extremely prolific process—in normal males, more than 1,000 sperm are generated per second. The cells driving this process are known as spermatogonial stem cells. However, in many men, the production of sperm does not occur at normal levels; more than 100 million men suffer from infertility globally, either as a result of genetics or as a side effect from chemotherapy. As such, spermatogonial stem cells are seen as a potential target for remedying male infertility.

Unfortunately, efforts to grow spermatogonial stem cells in a laboratory setting have generally failed. “There’s really two issues,” Dr. Miles Wilkinson, professor in the Department of Obstetrics, Gynecology and Reproductive Sciences at the University of California, San Diego (UC San Diego) School of Medicine, tells DDNEWS. “One is to keep spermatogonial stem cells alive. Our experience is that the cells with the characteristics of spermatogonial stem cells die after two or three weeks or so. This is something we are trying to improve on by changing culture conditions. The second problem is getting spermatogonial stem cells to...”

NEW OPTIONS WITH NITROGEN

Rice University researchers describe a novel chemical synthesis approach

BY KELSEY KAUSTINEN

HOUSTON—Ketones are natural carbon-based compounds that are a regular building block for chemical engineering, and the primary amino group (NH2)—which contains one nitrogen atom and two hydrogen atoms—is a functional group found in a...
sis, and determining new mechanisms for therapeutic intervention is obviously important. It will become the second leading cause of cancer deaths in the United States, and trying to understand mechanisms of drug resistance and new approaches to treatment are really needed."

The study featured in *Oncogene* details Witkiewicz’s research into how pancreatic cancer survives efforts to treat it with cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors such as palbociclib, ribociclib and abemaciclib, and explores a strategy for overcoming that resistance—combining CDK4/6 inhibitors with drugs inhibiting another growth-promoting kinase, MTOR.

"We demonstrate through our work here that many pancreatic cancers have intrinsic resistance to CDK4/6 inhibition and that we can overcome this resistance by taking advantage of its reliance on the MTOR pathway," wrote the authors. "Our findings from studies in many different cell lines and preclinical models show that combination treatment with MTOR and CDK4/6 inhibitors can be potent against many distinct types of pancreatic cancer."

The *Clinical Cancer Research* study establishes that conjoining chemotherapy treatment with cell cycle checkpoint inhibitors may effectively surmount the multiple ways that pancreatic adenocarcinoma tumors repel treatments.

"For this study, we exploited the replication stress that is known to be evoked by drivers of pancreatic cancer, in particular KRAS mutations," says Dr. Erik Knudsen, chair of Molecular and Cellular Biology at Roswell Park, an author on both studies. "We had to work through multiple unexpected resistance mechanisms of this notoriously recalcitrant cancer type, pancreatic adenocarcinoma, but ultimately were able to show that through coordinated targeting of cell cycle checkpoints with particular chemotherapy combinations, you can effectively control pancreatic tumors—which was an exciting and welcome result."

The Roswell Park team is developing clinical studies to further pursue both approaches, capitalizing on significant recent investments to better understand the specific biology of pancreatic cancers. They will explore these and other options in lab models to ensure they are identifying the best approaches for clinical use. They have been involved in previous clinical trials around pancreatic cancer and intend to develop new clinical trials based on the recently published research. In order to make an impact on pancreatic cancer outcomes, according

"We had to work through multiple unexpected resistance mechanisms of this notoriously recalcitrant cancer type, pancreatic adenocarcinoma, but ultimately were able to show that through coordinated targeting of cell cycle checkpoints with particular chemotherapy combinations, you can effectively control pancreatic tumors.”

Dr. Erik Knudsen of Roswell Park Comprehensive Cancer Center
**SPERM**

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expand in numbers. This is what you need to do ultimately for therapy: to go from a few cells—because spermatogonial stem cells seem to be relatively infrequent cells in the testes—to the point of having enough for therapeutic purposes. We and others in the field are working on this problem too." Identification of spermatogonial stem cells is an issue, Wilkinson adds, noting that researchers are currently dependent on gene markers to determine which cell clusters consist of spermatogonial stem cells.

Wilkinson and his UC San Diego colleagues recently published work in Cell Reports, in a paper titled “The Neonatal and Adult Human Testis Defined at the Single-Cell Level,” seeking to narrow in on more specifics about spermatogonial stem cells. Their work focused on single-cell sequencing to explore the genetics of the stem cells.

“Single-cell RNA sequencing determines the activity of hundreds of genes in the genomes of single cells,” said Wilkinson. “Because each cell type has a different combination of active genes, this technique allows new cell types to be identified. Applying this approach to the testis, we uncovered many different stages of sperm precursor cells in human testes.”

The team identified cell subtypes that potentially include spermatogonial stem cells, as well as biomarkers that define the stem cells. By analyzing neonatal testes, they were able to “map the timeline of male germ cell development from [primordial germ cells] through fetal germ cells to differentiating adult [spermatagonia] stages,” the authors noted.

The other key issue in the field, Wilkinson notes, is to figure out which cells with the characteristics of spermatogonial stem cells (SSCs) are actually stem cells. He tells DDNews that they intend to use a “functional stem cell test” to determine which of the various clusters of germ cells that they identified by single-cell RNA sequencing (as described in the recent paper) actually harbor the stem cells.

“Another contribution of our paper is the identification of cells next to the germ cells in the testis. The field calls them somatic cells. They are important because they are almost certainly making factors such as proteins that are critical for the germ cells to survive and proliferate,” says Wilkinson. “We identified several of the genes active in somatic cells that we think are important for encoding the proteins essential for the survival and expansion of germ cells. So now what we’re doing is trying to grow the human SSCs with the proteins encoded by these genes. Our single-cell sequencing analysis was critical because it gave us lots of candidate proteins we can try, looking for the holy grail, the key proteins that drive the survival and expansion of SSCs.”

**NITROGEN**

CONTINUED FROM PAGE 14

variety of chemical products. When ketones are functionalized with a primary amino group at the alpha carbon, it forms a primary alpha-aminoketone.

These compounds are important base constructs for creating pharmacologic products, as well as those for other applications such as farming fertilizers and pesticides. In research that will shorten the development steps necessary for such compounds, a team from Rice University shared news in February that they had engineered a one-step method for adding nitrogen to alpha-aminoketones.

The work, reported in a paper entitled “Alpha-Rubottom Oxidation: Synthetic Access to Primary α-Aminoketones,” was published last month in the Journal of the American Chemical Society.

“It’s a good precursor, because there’s no extra functionalization, like an acyl group, on the NH2 and it can then be converted to whatever you want,” explained László Kürti, an associate professor of chemistry and synthetic organic chemist at Rice University. “Previously, this was the issue: people would put nitrogen in there with extra functionality, but the further processing necessary to get to a free NH2 was complicated.”

“Oxygen is routinely put into the alpha position,” he said. “But nitrogen, no. We are the first to show this is possible in a large number of substrates, and it’s simple. It turns out that the solvent itself catalyzes the reaction.”

This new approach was discovered by postdoctoral researcher Zhe Zhou when he combined a silyl enol ether and a nitrogen source in hexafluoroisopropanol at room temperature. The resulting mixture was similar to Rubottom oxidation, a technique by which to oxidize enol ethers. Zhou and Qing-Qing Cheng, another postdoctoral researcher and co-author on the paper, refined this method and tested it further by creating α-aminoketones, three of which were synthetic amino acid precursors. Kürti called the latter “significant for drug design,” adding that “The enzymatic processes in living organisms are not going to attack them, because they don’t fit in the enzymes’ pockets.”

“Our amination method promises to replace a common three-step process to make alpha-aminoketones, and the yield, comparatively, is very good,” Zhou said. “In the standard process, each step cuts the yield, so one-step process is still superior even if the yields are identical, because it takes less time and there’s less risk of something going wrong. The last thing you want is to get eight steps from the beginning and then ruin it on the ninth because the conditions are not selective enough. Cutting steps is always beneficial in organic synthesis.”

In other molecular news out of the University recently, a team comprised of international researchers, including Rice materials scientist Edwin Thomas, made a new discovery regarding the formation of block copolymers. They learned that the left or right “chirality”—a property of asymmetry in which a molecule can’t be superposed on its mirror image, similar to the difference between your left and right hand—of a molecule is determined by the initial monomers of a polymer. Per the Rice press release, a “left-handed” molecule could be promising in drug development, while its chiral counterpart, the “right-handed” version, is toxic. In their work, the chirality of the copolymers “replicated itself as the microscopic material came together to form larger scale spiraling structures akin to those commonly found in nature,” as noted in a press release. The research appeared in the Proceedings of the National Academy of Sciences.

“From a properties standpoint, chirality is pretty big for optics,” Thomas said of their work. “The hope is that we can control self-assembly of chiral entities to make super-chiral entities to 10 or 100 times bigger so that they are able to interact with visible or even infrared light.” He added that the resultant polymers are elastic, and could potentially be engineered to react to certain wavelengths of light.

“We could make photonic crystals that reflect right-handed light and transmit left-handed light,” Thomas explained. “With circularly polarized light, it could transmit for one handedness and reflect for the other handedness. It would be a mirror for right and perfectly transparent for left.”
Harvard develops kidney organoid

Method for growing kidney organoids under flow enhances their vascularization and maturation

BY DONNEWS STAFF

BOSTON & CAMBRIDGE, Mass.—Increasingly essential for modeling human functions in the lab, manufactured mini-organs called organoids are grown in a culture dish, designed to contain many of the cell types and complex microarchitectures found in human organs. As Harvard University noted, they “have the potential to transform drug discovery, allowing researchers to experiment on samples of human tissue grown directly from patients.”

But because organoids are grown outside of a body, the university adds, “they lack the blood vessel structure, or vasculature, needed to circulate oxygen and nutrients, remove waste and send messages between different cell types. This has been a major roadblock in maturing groups of cells in a dish into truly functional tissues.”

For kidney organoids, this shortcoming has prevented researchers from emulating key kidney functions, such as blood filtration, reabsorption and urine production. Stem cell scientists have been working to create vascularized kidney organoids that are robust enough to enhance renal drug toxicity testing and, ultimately, lead to new building blocks for renal replacement therapies. But now there is a new approach, published in Nature Methods and developed by a Harvard University-led team, demonstrating how organoids can be vascularized, opening the door to a flood of possibilities in stem cell research.

The work was led by Drs. Jennifer Lewis and Ryuji Morizane, with a team of scientists at the Harvard Stem Cell Institute (HSCI), the Harvard John A. Paulson School of Engineering and Applied Sciences (SEAS), Brigham and Women’s Hospital and the Wyss Institute for Biologically Inspired Engineering.

Their bioengineering approach exposes stem cell-derived organoids to fluidic shear stress—that is, the frictional force of flowing biological fluids. Using this technique, researchers were able to expand organoid-derived vascular networks significantly. Compared with previous, static culturing methods, the exposure improved the maturation of kidney compartments.

In 2015, Morizane and fellow HSCI faculty member Dr. Joseph Bonventre developed a method that enabled them to derive 3D kidney organoids from human pluripotent stem cells.

“While our organoids and those generated in other laboratories contained large numbers of well-organized nephrons and primitive blood vessels, they still lacked perivascular compartmental components with perfusable lumens,” said Morizane, who is also an assistant professor at Brigham and Women’s Hospital and Harvard Medical School.

More recently, researchers around the world have matured kidney organoids by implanting them into animals, where they can connect directly to the host’s vasculature.

“For the first time, our study demonstrates that by exposing growing organoids to fluid flow, a mechanical cue known to play an important role for tissue development in the body, we can greatly enhance their vascularization and maturation in vitro,” noted Morizane.

To accomplish this feat, the team used expertise from the Lewis lab that has pioneered strategies to create vascularized human tissues, including 3D kidney-on-chip models. These strategies use 3D bioprinting that can be perfused and sustained for long durations. Building on this work, the team explored the idea that fluid flow could also promote the formation of blood vessels from precursor endothelial cells found in growing kidney organoids.

“We determined the right combination of underlying extracellular matrix, media additives, and fluidic shear stress under which human stem-cell derived organoids would flourish when grown in our 3D-printed microfluidic chips,” said Dr. Kimberly Homan, who is a co-first author on the study with Dr. Navin Gupta.

“The vascular networks form close to the epithelial structures that build the glomerular and tubular compartments, and in turn promote epithelial maturation. This integrated process works really like a two-way street,” added Gupta.

Homan is a research associate in Lewis’ group at the Wyss Institute and SEAS, and Gupta is a clinical research fellow working on Morizane’s team at the Brigham.

The vessels growing on the 3D-printed chips formed an interconnected network with open lumens. The network could be perfused with fluids, as confirmed by directly imaging fluorescent beads moving freely through them.

“This important advance opens up new avenues for accurately testing drug toxicity in vitro in differentiated nephron compartments and modeling kidney diseases, like polycystic kidney disease, that affect specific structures and cell types using patient-derived stem cells as the starting point,” Lewis commented. “Our method may pave the way to also vascularize other types of organoids, such as the liver organoids.”

A decline for R&D

Research and development returns fall to lowest level in nine years

BY DONNEWS STAFF

LONDON—Projected returns on investment in research and development (R&D) for the top 12 biopharmaceutical companies have fallen to 1.9 percent, according to a study by Deloitte’s Centre for Health Solutions leveraging revenue forecasts and industry benchmarks generated by GlobalData, a leading data and analytics company.

The study, entitled “Unlocking R&D productivity: Measuring the return from pharmaceutical innovation 2018” and published by Deloitte, found that average returns are down 1.8 percentage points from 3.7 percent in 2017, and forecast average peak sales are at $408 million, making 2018 the lowest since Deloitte’s first R&D report in 2010. In the rapidly changingbiopharma landscape, R&D returns have dropped by 8.2 percentage points from 10.1 percent in 2016.

The increase in average cost of development of biopharmaceutical drugs is a driver of this declining return. Average costs of development before regulatory approval for commercialization have increased in six out of the last eight years, with the average cost now at $2.18 billion, compared to just under $1.19 billion in 2010.

The study also confirms that a systemic approach to productivity improvement by innovative streamlining approaches, is needed to lessen development costs and timeline, ultimately increasing R&D returns. Companies need to act now and embrace new ways of working, embed new technologies, such as artificial intelligence and robotic process automation, and seek out talent with the right skill sets to optimize their return on investment in pharmaceutical innovation, say Deloitte and GlobalData.

“The good news is that advances in these technologies are already starting to have an impact in R&D. Companies will increasingly use AI, in particular machine-learning algorithms, to reduce R&D cycle time, costs and ultimately build a strong and sustainable drug pipeline,” commented Dr. Bonnie Bain, global head of pharma at GlobalData. “We will also continue to see use of AI extend beyond drug discovery and lead optimization to playing an important role in clinical trials—not only for analyzing the large amounts of data being generated from clinical studies, but also for trial recruitment and management.”

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SPECIAL REPORT

Immunology & Autoimmunity

TURN OF THE COIN

Many of the mechanisms being perturbed to treat cancer are the same mechanisms the body uses to avoid self-harm in the form of reactivity to autoantigens and the development of autoimmune diseases, such as Hashimoto’s thyroiditis as depicted here.

Treading the edge between autoimmunity and oncology

BY RANDALL C WILLIS

UMORS AND INFECTIOUS MICROBES have been remarkably successful at evading the human immune system, co-opting molecular mechanisms to dampen the ability of immune cells to see them as anything other than ‘self.’

At least for the former, this understanding has led to an explosion of efforts to reverse this cloaking device, to help the immune system identify and fight the tumor cells as unwelcome foreigners. Therapeutic antibodies, cytokines, chimeric antigen receptor T (CAR-T) cells and checkpoint inhibitors have been leveraged to make inroads against various cancers, giving birth to the field of immuno-oncology.

At the same time, many of the mechanisms being perturbed to treat cancer are the same mechanisms the body uses to avoid self-harm in the form of reactivity to autoantigens and the development of autoimmune diseases like rheumatoid arthritis, psoriasis, multiple sclerosis and lupus.

“Tumors and infectious microbes have been remarkably successful at evading the human immune system, co-opting molecular mechanisms to dampen the ability of immune cells to see them as anything other than ‘self.’”

“One is that every major adverse event when you have practiced checkpoint therapy has been self-reactive in nature, “ he explains. “What that tells me, as an immunologist, is that all or most of us may harbor self-reactive T cells within us, and that they are held in check by the ‘self-culture’ that we are exposed to.”

Suri notes that while checkpoint therapy has been instrumental in informing the autoimmune landscape, in terms of both the technological insights into the immune system as well as the pathophysiological yin-yang that each condition represents.

“Treading the edge between autoimmunity and oncology is a balancing act, with the potential for both therapeutic and side effects.”

“Autoimmunity is a complex interplay between genetics, environment, and epigenetics. Autoimmune disorders are not just the result of a single trigger, but a combination of factors that interact in a patient-specific way.”

Suri emphasizes the importance of understanding the underlying mechanisms of autoimmunity and how they intersect with oncology.

“By studying the molecular pathways that govern immune responses, we can gain insights into how to modulate these responses to treat both cancer and autoimmune diseases.”

Suri believes that by integrating the insights from the field of immuno-oncology, researchers can develop more targeted therapies for autoimmune disorders.

“Immunotherapy has transformed the landscape of cancer treatment, and these same principles can be applied to autoimmune diseases. By harnessing the power of the immune system, we can achieve therapeutic benefit while minimizing side effects.”

Suri and his team at Cue Biopharma are working on developing therapies that target specific immune pathways to treat autoimmune disorders.

“Autoimmune diseases are a major unmet medical need, and we are excited about the potential of immuno-oncology to inform our understanding and development of new treatments.”

Suri concludes that the field of immuno-oncology is still in its infancy, but the promise of harnessing the immune system for the benefit of patients is exciting.

“For both cancer and autoimmune diseases, the goal is to achieve a state of balance between the immune system and the body’s cells. By understanding how the immune system—and the body’s cells—itself—works, we can develop therapies that not only treat but also cure.”

Suri believes that the future of autoimmunity is bright, and that the insights gained from immuno-oncology will be instrumental in advancing the field of autoimmune diseases.
in check by the similar mechanisms that the tumor is co-opting for anti-tumor T cells.”

In other words, he reframes, everybody has the potential to break tolerance. Thus, for those patients who develop cancer and receive treatments that might block the mechanisms of peripheral tolerance like anti-CTLA-4 or anti-PD-1, there is a risk of developing an autoimmune disease.

“And that’s what happens when you look at the knockout phenotypes,” Suri says. “In a CTLA-4 knockout in the experimental animals setting, the pups are dead by three to four weeks of age from systemic inflammation.”

“The other thing that is important is that the onset of the autoimmune adverse event has no bearing on whether you have a tumor response or not,” he presses. “Those are independent events.”

“From the patient’s perspective, that may not be desirable, because not only are you taking a gamble with hoping that you raise an anti-tumor response, but you may actually end up worse if you only get the autoimmune aspect with no benefit from the antitumor aspect.”

So, how do you develop a therapeutic platform that allows you to activate the immune system when fighting cancer, while also tightly controlling the immune system when it goes awry?

For many companies and research groups, the answer arises from immuno-oncology and the development of modular immuno-therapy platforms.

“If you target a receptor to activate something, you could very well envision blocking it to inhibit something,” explains Jane Gross, chief scientific officer of Aptevo Therapeutics. “You could actually target the same receptors, just differently for treatment of the different cancers or autoimmune diseases.”

ONE MOLECULE, TWO COMPONENTS

According to Dan Passeri, Cue Biopharma’s CEO, the company’s Immuno-STAT platform is both conceptually and etymologically tied to the idea of a rheostat, something with the ability to control up and down by exploiting, in their case, the same biology.

The platform, which the company is developing for both autoimmune and immuno-oncology indications, involves two components: one that targets the cell of interest via its antigen (or autoantigen) and a second that serves to stimulate or inhibit target cells depending on the disease you are treating.

Both Suri and Passeri are quick to credit the system design to Albert Einstein College of Medicine’s Steve Almo, who is a protein engineer and not an immunologist.

“The reason that is relevant is he was not contaminated with preconceived notions of how to combat cancer, looking at the tumor micro-environment, etc.” Passeri reasons. “He just looked at the question of how to modulate the immune system via T cells, taking advantage of the exquisite selectivity that is there with the T cell receptor to design a molecule that can dock at the T cell receptor and deliver a co-stimulatory molecule concurrently.”

This emulates the way that antigen-presenting cells interface with T cells.

“It is a very modular approach that allows us to have a tremendous amount of versatility in terms of dialing in and dialing out certain features so that we can design molecules and optimize them based on what we’re trying to achieve,” Passeri enthuses.

Last summer, Cue announced it had generated the first autoimmune Immuno-STAT molecule as part of its collaboration with Merck.

As Suri explains, Merck had IMMUNE CONTINUED ON PAGE 20

Jane Gross, chief scientific officer of Aptevo Therapeutics
**IMMUNE**

Continued from page 11

expressed interest in two select indications, but he is not liberty to elaborate on what those are, other than to say that they are “well-recognized autoimmune diseases where there is a very strong MHC association.”

Once you’ve targeted the offending T cell, he continues, you can either try to purge them from the immune repertoire or, as is the case at Cue, convert them in vivo from a pathogenic to regulatory phenotype.

This approach, he argues, provides “selective disease-specific regulation without broad dampening of the system as one would see potentially with anti-cytokine antibodies or anti-CD8 or things like that which just dampen the whole compartment.”

Other groups, he suggests, are attempting the Treg (regulatory T cell) approach but ex vivo, removing T cells from the body, converting their phenotype and then reintroducing them, but, as he warns, with no idea of T cell receptor specificity.

Aptevo Therapeutics is taking a similar approach to Cue’s with its ADAPTIR platform, where the co-stimulatory component is the cytokine IL-10.

As Jane Gross explains, cytokines are pleiotropic in that they can both up- and down-regulate various activities in the immune system, making them both attractive but potentially risky targets.

“What people have started to realize in the last four or five years is that you can create a bispecific that targets the cytokine in a specific way,” she says.

“Some have attached cytokines to antibodies,” she reports. “Other people have PEGylated them in a particular way, so they target a specific set of receptors and they increase the half-life.”

“We prefer the strategy of recombinantly fusing a cytokine to a structure that has the antibody-like modality,” she notes. “The antibody provides a delivery system, the cytokine provides an increased half-life, the ability to manufacture in a particular way, and the targeting arm targets it to a specific cell type, or you could target to a specific receptor.”

This approach is the basis of the company’s autoimmune lead APVO210.

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This approach is the basis of the company’s autoimmune lead APVO210.

“With APVO210, what that drug has allowed us to do is target IL-10 to a particular set of cell types, which are more appropriate for down-regulating the immune system,” Gross explains.

APVO210 targets the myeloid and dendritic cell lineages, and not lymphocytes,” she continues.

“The myeloid and dendritic cell lineages are the relevant population to shut down the pathogenesis of the disease.

“The lymphocytes are the ones that would rev up the immune system, so by eliminating that, it is beneficial for autoimmune disease.”

Another part of that equation is a specific type of regulatory T cells known as Tr1, which are dedicated to maintaining immune tolerance. As a first step, Stanford University’s Maria Grazia Roncarolo and colleagues demonstrated last year that APVO210 was able to differentiate CD4+ monocytes in vitro into tolerogenic dendritic cells. These dendritic cells were able to induce Tr1 cells, which inhibited primary T cell proliferation.

“The specific ability of APVO210 to deliver IL-10 to CD8+ cells, as compared to IL-10 [alone], which has a pleiotropic effect, may have significant advantages for in vivo use,” the authors wrote. “The systemic administration of IL-10 in vivo has indeed been limited by the development of adverse effects that are due to its stimulatory functions on CD8+ T cells and B cells.”

They further added, “We hypothesize that the in vivo use of this molecule could decrease the risk of triggering specific T- and B-cell responses associated with IL-10 systemic delivery, and, therefore, lead to more targeted and safe control of undesired inflammatory and autoimmune responses.”

Similar to Aptevo’s cytokine approach, VIB-Ugent’s Jan Tavernier, co-founder of Orionis Biosciences, and colleagues recently described a targeted approach to controlling immune cells, but in this case, the cytokine was type 1 interferon (IFN) rather than IL-10.

Their platform, known as AcTaferons (AFNs) or activity-on-target IFNs, consists of a mutant IFN with reduced receptor affinity targeting IFNs, consists of a mutant IFN with reduced receptor affinity coupled either to a camelid antibody or a ligand that selectively recognizes a cell-specific surface marker.

The researchers tested their platform in experimental autoimmune encephalitis (EAE), a mouse model of multiple sclerosis, noting significant mortality and hematologic deficits in the mice.

Targeting their AFN to Cleca9+ dendritic cells, in contrast, significantly protected the mice without the noted side effects. In fact, Cleca9-AFN offered long-term protection from progression and the development of paralysis even when mice were dosed after disease onset.

They also noted that Treg cell numbers increased in Cleca9-AFN-treated EAE mice and that the percentage of Tregs producing IFN-γ and TNF-α was significantly increased.

“Our results indicate that targeting IFN activity to DCs in patients via a novel therapy for MS and other autoimmune diseases, and clinical trials are being set up,” they wrote, acknowledging data supporting this approach.

“Needless to say, these therapeutic cell-based strategies are extremely laborious, time-consuming, and entirely personalized, and challenging obstacles and pitfalls are associated with the in vivo generation of tolDCs,” they cautioned.

“Hence, we speculate that targeting IFN activity to DCs in patients using AFNs may induce systemic tolerization and provide a novel therapy for MS, in contrast to cell-based DC transduction.”

For JDRF/Wellcome Diabetes and Inflammation Laboratory’s
As Amgen notes of bispecific antibodies, one challenge in making them is getting cells to assemble the pieces of the antibody correctly. Antibodies are modular in nature. When cells are asked to incorporate subunits from two different antibodies into one structure, they generate 10 configurations, and just one has the correct and functional format. To solve this problem, scientists at Amgen have engineered antibodies with positive and negative electrical charges inserted at key points (indicated by + and - signs). This approach reportedly ensures that the correct subunits are attracted to each other while incorrect pairings are repulsed. The key result, the company says, is a process that generates fully functional bispecific molecules, a major step in advancing this highly promising drug modality.

“The attractive nature of a bispecific and the immune system is that once you get a platform technology developed, you can use it in different ways and exploit the knowledge of basic research to tweak either positively or negatively. We have entertained the idea of now taking cytokines and fusing them to an ADAPTIR structure for oncology.”

Jane Gross, chief scientific officer of Aptevo Therapeutics

Linda Wicker and colleagues, the cytokine of interest was IL-2, taking a nod from recent studies showing that low-dose recombinant human IL-2 (Proleukin) reduced disease activity in patients with systemic lupus erythematosus (SLE).

Like the other efforts, to optimize the desired effects of the cytokine, the researchers mutated IL-2 to significantly reduce its ability to activate CD4+ and CD8+ effector T cells and natural killer cells, while only modestly reducing its ability to activate Tregs. They then coupled this IL-2 mutein, as they described it, to an effector-silent IL-2 mutein, as they described it, to an effector-silent coupled this IL-2 mutein, as they described it, to an effector-silent cytokine and fusing them to an ADAPTIR structure for oncology.

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“I think the applicability is potentially to block a checkpoint inhibitor and induce an activation at the same time,” she says. “And you can do it either in trans or in cis, so either between two cells or on one cell.”

Just as immuno-oncology has not limited itself to protein therapeutics, neither has the autoimmunity field, which is also exploring cell-based approaches to reversing autoantigen reactivity.

BEYOND BIOMOLECULES

Late last year, Zhenhua Dai and colleagues at Guangdong Provincial Hospital of Chinese Medicine reviewed the current state of efforts to use CAR-T approaches to Tregs in the hope of inducing immunologic tolerance.

They recounted one effort showing that CAR-Tregs specific for trimetrexate (TNF), an antigen commonly used to generate mouse models of colitis, was able to suppress effector T cell proliferation whereas control Tregs could not. “When colitis was induced with 2,4,6-trinitrobenzene sulphonic acid (TNBS), the mortality rate of...”
A field that is emerging but is not our core area of focus is the interplay between the microbiome and the immune response, be it autoimmune or cancer immunotherapy,” Suri explains. (See also the January 2019 DDNews “Special Report on Microbiomics: Army of One.”)

In particular, he points to the concept of molecular mimicry, where a microbial epitope cross-reacts with a natural epitope (self) in the host. Thus, when the body responds to infection, the normally quiescent autoreactive T cells are activated and attack not only the infectious microbes, but also any tissues expressing (self) in the host. Thus, when the concept of molecular mimicry, on Microbiomics: Army of One” .)

Increasingly, researchers are also scanning the microbes of autoreactive T cells that are growing body of evidence linked to rheumatoid arthritis. “From a scientific point of view, you can identify way more detail and get way more information with a peptide microarray compared to an ELISA or a western blot. [But] what we see on the microarray can usually be translated into a standard ELISA format,” says Volker Stadler, CEO of PEPperPRINT.

Stadler sees the diagnostic opportunities for the peptide microarray as slowly evolving. “From a scientific point of view, you can identify way more detail and get way more information with a peptide microarray compared to an ELISA or a western blot,” he says, but then cautiously that this increased information comes at the cost of a more technologically sophisticated platform. Rather, he sees the peptide microarray and ELISA as interconnectable. “What we see on the microarray can usually be translated into a standard ELISA format,” he explains.

Stadler also echoes the opportunities for patient stratification afforded by an understanding of epitopes and reactivity, offering an example from immunology. “You can generate peptide microarrays that contain a number of tumor-related antigens translated into overlapping peptides for epitope mapping,” he says. “What you could do in addition is translate the sequencing data from a patient into peptide pairs against IgG, and then you could use the peptide pairs to ask how the immune system is reacting against the tumor-related antigen or even the patient-specific neopeptides,” he enthuses.

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The researchers identified IgG reactivity to conserved A/T hook domains within the EBV proteins EBNA-1 and BALF-2 recombinants which are related to host DNA-binding proteins such as RAG-1 recombinase and histones, as well as reactivity to the EBV-encoded vireno BCRF1, an IL-10 homologue. Preliminary data obtained from the immune response to some shared gene-encoded proteins reported in this work suggest that EBV-encoded gene-encoded proteins such as BZLF1 and EBNA-1 are highly antigenic and thus trigger IgG against wild proteins, other EBV-encoded shared genes such as virenoes may be poorly antigenic, permitting the viral-encoded projects to function as antagonists or partial agonists of the host immune response,” the authors noted.

Beyond the specific reactivities, Ivan also wondered about the implications of such proteomic assays for disease diagnosis and treatment monitoring.

“Using inexpensive and highly automated molecular fingerprints, it might be possible in the future to identify patients at risk of autoimmune syndromes prior to development of symptoms based solely on their response to specific epitopes in viral proteins and shared host proteins,” they concluded.

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Aptivo Therapeutics has put a strong focus on its ADAPTIR platform, where the co-stimulatory component of the therapeutic is the cytokine IL-10. As the company’s chief scientific officer, Jane Gross, explains, cytokines are pleotropic in that they can both up- and down-regulate various activities in the immune system, making them both attractive but potentially risky targets.

Surveying the landscape, Dai and colleagues suggested that antigen-directed CAR-Tregs were likely to generate fewer side effects than blanket immunosuppression and were obviously more specific than polyclonal Tregs, but they also cautioned that antigen selection could be significantly challenging. Furthermore, incidences of cytokine storm or neuronal toxicity have been noted with anti-tumor CAR-T cells.

Pharmicell’s MiYoung Park and colleagues took cellular intervention one step broader, looking at the application of myeloid-derived precursors cells (MDSCs) to treat psoriasis in the imiquimod (IMQ) induced mouse model. MDSCs are known to release many immunosuppressive mediators such as IL-10, TGF-β and prostaglandin E2 as well as induce Treg cells. They noted that MDSC injection significantly reduced inflammasome responses in imiquimod-treated mice and inhibited the release of pro-inflammatory cytokines associated with psoriasis. Likewise, there was a dose-dependent increase in Tregs and a concomitant decrease in immunosuppressive T helper cells (Th, Th7).

The findings are consistent with similar work in murine models of arthritis and SLE. “Taken together,” the authors concluded, “these results imply that MDSCs have immunomodulatory and immunosuppressive effects on disease progression in a murine model of psoriasis and that MDSCs could be used as preventive or therapeutic strategies for the management of autoimmune inflammatory skin disorders, such as psoriasis.”
SPECIAL REPORT

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The American Association for Cancer Research (AACR) heads to Atlanta, where it will host its 110th Annual Meeting from March 29 to April 3 at the Georgia World Congress Center. The AACR Annual Meeting 2019 has an anticipated attendance of more than 22,500 scientists, clinicians, advocates and other attendees from around the world, and brings together what AACR calls “the best talent and job opportunities in cancer and biomedical research.”

“The AACR Annual Meeting program covers the latest discoveries across the spectrum of cancer research—from population science and prevention; to cancer biology, translational and clinical studies; to survivorship and advocacy—and highlights the work of the best minds in research and medicine from institutions all over the world,” says AACR’s meeting website.

“The AACR annual meeting is the meeting that we all look forward to very year,” says Dr. Elizabeth M. Jaffee, AACR’s 2018-2019 president, in a welcome/preview video for the meeting. “It’s a meeting that brings experts from all sectors of the cancer community—from government, academia, the pharmaceutical industry, survivorship, patients, patient advocates. It brings everyone together at one meeting. It’s a huge meeting. The best science—the most up-to-date science—is presented, from basic to translational to clinical care.”

With this year’s theme, “Integrative Cancer Science • Global Impact • Individualized Patient Care,” the scientific program includes a roster of world-class speakers, hundreds of invited talks and more than 6,000 proffered papers. Presentations at the AACR Annual Meeting will span the entire field of cancer research, highlighting basic, translational and clinical research on important topics such as immunotherapy, science policy, targeted therapy, artificial intelligence, liquid biopsy, early detection, cancer interception, prevention, survivorship and cancer health disparities. This year’s meeting will also include a number of science policy sessions. Those following the meeting on social media

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Dr. Elizabeth M. Jaffee, AACR’s 2018-2019 president
can join the conversation on Twitter with the hashtag #AACR19.

“At this year’s AACR annual meeting in Atlanta, there will be an extensive focus on the science of cancer health disparities, including a plenary session dedicated to this important topic,” says Dr. John D. Carpten, the 2019 program chair for the AACR meeting, in AACR’s welcome/preview video. “In addition, we will offer a wide range of educational and scientific sessions covering the entire spectrum of cancer health disparities and research.”

As Jaffee told DDNews, AACR added a new session format this year, and two special sessions on “Making Science Count for Patients” will focus the story of basic science discoveries on “Making Science Count for Patients.”

Dr. Elizabeth Jaffee and AACR Past-President Dr. Michael Caligiuri at the AACR Annual Meeting National Cancer Institute Director Dr. Norman E. “Ned” Sharpless speaks with AACR President Dr. John D. Carpten and AACR Past-President Dr. Michael Caligiuri at the AACR Annual Meeting 2018 in Chicago.

Another new feature of this year’s meeting is the addition of two major sessions to highlight the work of these rising stars.” (See also the “NextGen Stars” sidebar here.)

The AACR Annual Meeting Online Program Planner is currently available so that users can browse and search all sessions and presentations by author, title, session type, or track/organ site. Meeting registrants will be able to log in and create a personal itinerary.

“The AACR is the oldest and largest scientific organization in the world, focused on every aspect of high-quality, innovative cancer research. Its reputation for scientific breadth and excellence attract the premier researchers in the field,” notes AACR’s website. “The programs and services of the AACR foster the exchange of knowledge and new ideas among scientists dedicated to cancer research, provide training opportunities for the next generation of cancer researchers, and increase public understanding of cancer.”

Or, as Jaffee elaborates in the welcome/preview video: “We get to network with individuals that it’s hard to meet with at other times in the year. You get to network with groups that you may be collaborating with, you get to network with groups where you can form new collaborations. You get to interact with young people—young people who are interested in cancer research; who may be interested in coming and working in your laboratory someday or may be interested in their first job with you. So it’s just an opportunity for the whole community internationally to get together, network, interact, share information—and the hope is that by doing this, we’re really making big progress in the future of cancer research.”

Another new feature of this year’s meeting is an additional day of educational programming, which will begin on Friday, March 29, at 3 p.m. and continue through Saturday, March 30. More than 60 unique Educational Sessions and Methods Workshops are included in this program, and sessions are open to all meeting registrants. The Opening Ceremony and the Opening Plenary Session will take place on Sunday morning, March 31.

“Don’t miss this opportunity to join more than 25,000 of your colleagues from around the globe in order to network with the greatest minds in cancer research,” urges Carpten.
UNRAVELING THE PATH TO DRUG DISCOVERY

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FcRn Studies
Assess therapeutic antibody half-life using our FcRn platform

STUDY READY COHORTS
Humanized Mice
PDX Mice
FcRn Mice

FFPE PDX SLIDES
Utilize biomarker assays to screen your tissue sample

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Apply JAX scientific knowledge— we have a thorough understanding of the complex biology and mechanisms in these models

don’t have it...
need better data...
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EFFICACY STUDIES
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Utilize the JAX PDX platform to obtain translationally-relevant data

HUMANIZED MOUSE STUDIES
Leverage this platform to simulate trials, or evaluate multiple drugs alone or in combination

FCRN STUDIES
Assess therapeutic antibody half-life using our FcRn platform

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FcRn Mice

FFPE PDX SLIDES
Utilize biomarker assays to screen your tissue sample

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DETERMINE EFFICACY
need a different target...

don't have it...

IMPROVE MODEL
Model Generation Services
PDX Repository

STUDY DESIGN REVIEW
Select New Biomarker Readout
Study Changes

ON TO THE NEXT PHASE

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CAREER AND ADVANCEMENT

PROFESSIONAL AND CAREER ADVANCEMENT SESSIONS
Professional and Career Advancement Sessions are organized to provide important skills to investigators at all levels, from high school students to senior faculty. Programs for high school students and undergraduates require registration. All other Professional Advancement Sessions are available to Annual Meeting registrants free of charge, but attendance is limited to AACR members.

PROFESSIONAL ADVANCEMENT SESSION/WEBCASTS
As an additional member benefit, webcasts of selected Professional Advancement Session presentations are now available free to AACR members. Members who have already created a webcast portal account can log in and view these sessions. Members who do not have a webcast account can create an account to begin viewing the career development webcasts. The following 2018 Professional Advancement Session presentations are available to members as free webcasts:
- The Critical Role of Physician-scientists in Advancing Cancer Science
- Challenges and Solutions for Wonder Women in Science
- Getting Hired!
- Women in Cancer Research Career Mentoring Session
- Logistics of Starting a Laboratory

AACRCENTRAL: NETWORKING, RESOURCE, AND CAREER CENTERS
At the crossroads of the Exhibit Hall, AACRCentral is your one-stop source for information on and assistance with all AACR programs, whether you need to ask a question, find a job, check your email or meet up with a colleague.

MICR NETWORKING AND RESOURCE CENTER
The Minorities in Cancer Research (MICR) Networking and Resource Center hosts exciting meet-and-greet opportunities with prominent investigators and provides meeting attendees with a comfortable and social environment for networking one-on-one and in small groups. All MICR members and Annual Meeting registrants are encouraged to visit the MICR Networking and Resource Center to learn about AACR and MICR programs, awards, funding and more.

WICR NETWORKING AND CAREER CENTER (AMRC)
The Women in Cancer Research (WICR) Networking and Resource Center is the location for networking with members of the WICR Council, WICR Scholars and members of WICR. All Annual Meeting attendees and WICR members are invited to use the Center during exhibit hours for networking, and to learn more about professional advancement opportunities and other programs of interest.

ASSOCIATE MEMBER RESOURCE AND CAREER CENTER (AMRC)
The Associate Member Resource and Career Center, organized by the Associate Member Council (AMC), is open to all graduate students, medical students and residents, and clinical and postdoctoral fellows, regardless of membership status. The Center provides an informal place for early-career scientists to connect with colleagues, plan their time at the meeting and learn about programs and other professional advancement opportunities. The AMC Meet and Greet is also held in this location.

AACR AMPHITHEATER
The AACR Amphitheater hosts a variety of sessions, including the AMC-organized sessions for early-career scientists, “Meet the AACR CEO,” and “Meet the AACR President.” All sessions provide a special opportunity for interactive discussion in a small group setting to discuss career paths and vision for the future of the field. All sessions are free; seating is available on a first-come, first-served basis.

AACR MEMBERSHIP CENTER
The AACR Membership Center provides a place where members can obtain information regarding their membership, join Association groups within the AACR, update contact information, pay annual dues, transfer categories of membership and become familiar with new membership services. Nonmembers are encouraged to visit the Membership Center to submit an application for membership. The AACR is eager to support the exchange of knowledge and research with investigators who are located in countries with emerging economies. (Significantly reduced membership dues are available for these investigators.)

AACR 2019 Cancer and Biomedical Research Career Fair
The AACR 2019 Cancer and Biomedical Research Career Fair is an excellent place to find out about some of the latest products, services and breakthroughs, as well as to interact with colleagues.

PLENARY SESSIONS

PL01: Opening Plenary: Achieving Equitable Patient Care through Precision and Convergent Cancer Science
Physician vs. physician: Digitizing clinical assessment, and using it for evidence-based prediction of outcomes
Peter Kuhn, Jorge J. Nieva
Physician vs. physician: Digitizing clinical assessment, and using it for evidence-based prediction of outcomes
Jorge J. Nieva, Peter Kuhn
Therapeutic implications of DNA repair defects in cancer
Alan Ashworth

Defining the actionable genome
David B. Solit
Precision oncology: The path forward
Levi A. Garraway
Next-generation CAR T cells designed to overcome tumor resistance
Crystal L. Mackall
Role of immune profiling and T cell exhaustion in the response to immunotherapy in cancer
E. John Wherry

PL02: Clinical and Translational Research in Diverse Populations
Colorectal cancer in Nigeria: High tech and low-tech approaches to improving patient outcomes
Olusegun I. Alatise
Spliceomics: Alternative RNA splicing as a source of ancestry-related molecular targets in precision oncology and cancer disparities
Steven R. Patierno

The DARC side of breast cancer disparities: Links to African ancestry and immunologic tumor responses
Melissa B. Davis
Genomic and epigenomic studies of cholangiocarcinoma in diverse populations
Bin Tean Teh

PL03: Manipulating the Immune System in Cancer Therapy
T-cell therapy targeting unique cancer mutations
Steven A. Rosenberg
Redirecting T-cells for cancer immunotherapy using next generation bispecific antibodies and fusion proteins
Pablo Umans
Taming the beast: Strategies to target the immune suppressive macrophage to enhance cancer immunity
Judith A. Varner
Mismatch repair deficiency: A connection between the immune system and cancer genetics
Dung T. Le

PL04: Pathogen-Related Cancers: Implications for Populations and Public Health
Screening for nasopharyngeal carcinoma using plasma Epstein-Barr virus DNA: Technological and clinical insights
Yuk Ming Dennis Lo
Hepatitis B and C virus-related hepatocellular carcinoma in the era of highly active antiviral therapies
Jean-Michel Pawlotsky

HIV malignancies: From despair to gene therapy
Ariela Novick
Therapeutic vaccination to treat HPV disease: Lessons learned from high grade intraepithelial lesions
Cornelia L. Trimble

PL05: AACR Annual Meeting 2019 Highlights: Vision for the Future
Prevention, Early Detection, and Interception
Marcia R. Cruz-Correa
Basic Cancer Science and Translational Research
John D. Carpten
Clinical Research and Clinical Trials and Therapeutics
Patricia M. LoRusso
Wrap-up and Vision for the Future
Elaine R. Mardis
PHILADELPHIA — An analysis of cervical precancers over a period of seven years showed that two strains of human papillomavirus (HPV) that have been targeted by vaccination since 2006 have declined, accounting for a smaller proportion of cervical disease, according to results published in Cancer Epidemiology, Biomarkers & Prevention. The study offers evidence that Human Papillomavirus (HPV) vaccination has reduced the incidence of infections that can lead to cervical cancer, said the study’s lead author, Dr. Nancy McClung, an epidemic intelligence service officer at the Centers for Disease Control and Prevention (CDC) in Atlanta.

“Almost all sexually active individuals will get HPV at some point in their lifetime, but most HPV infections go away on their own without any treatment,” McClung explained. “If an HPV infection does not go away, it can cause cell changes over time, develop into a lesion on the cervix called a cervical precancer. Cervical pre-cancers allow us to observe the impact of HPV vaccination earlier than cervical cancer, which can take decades to develop.”

Previous research has suggested that the incidence of cervical precancer has been decreasing. In this study, researchers sought to determine whether HPV types 16 and 18, which are responsible for approximately 70 percent of cervical cancers worldwide, are also decreasing. These two types have been targeted by the quadrivalent HPV vaccine, which was most typically administered in the United States between 2006 and 2015, and by the 9-valent HPV vaccine currently administered in the United States.

As part of the CDC’s HPV Vaccine Impact Monitoring Project (HPV-IMPACT), McClung and colleagues analyzed more than 10,000 archived specimens collected between 2008 and 2014 from women aged 18-39 who had been diagnosed with grade 2 or 3 cervical intraepithelial neoplasia adenocarcinoma in situ (CIN2+).

Researchers noted that every 4 years, more women are vaccinated during early adolescence and before exposure to HPV. “This is clear evidence that the HPV vaccine is working to prevent cervical disease in young women in the United States,” McClung concluded. “In the coming years, we should see even greater impact as more women are vaccinated during early adolescence and before exposure to HPV.”

Methods Workshops

SATURDAY, MARCH 30

- BRCAl Variants of Unknown Significance (VUS): New Vistas in the Assessment of Cancer Risk
- Clinical Trial Design: Part 1: The ABCs of Doing Cancer Clinical Trials
- Clinical Trial Design: Part 2: Novel Trial Designs
- Clinical Trial Design: Part 3: Biomarker-Directed Clinical Trials
- Clinical Trial Design: Part 4: Deciphering and Targeting Lysosomes in Cancer
- Designing Biomarker Studies to Achieve Desired Clinical Applications
- Methods for Utilizing the Microbiome in Cancer Epidemiology Research
- Methods to Study Metabolism in Cancer Research
- Modeling Tumor Dormancy
- Novel Imaging Strategies in the Metastatic Niche
- Sample Size and Power Workshop for Basic, Translational, and Clinical Studies

### Educational Sessions and Methods Workshops

#### Education Sessions

**FRIDAY, MARCH 29**

- Biomarker Studies: Study Design and Statistical Considerations
- Genetic Predispositions to Childhood Leukemias: Implications for Pathogenesis and Screening
- Host versus Tumor Autophagy in Cancer
- Immune-Targeted Biomarker Incorporation into Therapeutic Decision Making
- Integrating Tumor Immunology and Molecular Epidemiology
- Interaction of Radiation and Immune Therapy
- Modulation of the Gut Microbiome to Treat Dysbiosis and Cancer
- Molecular Pathology for Cancer Researchers: Present and Future
- Preleukemia and Clonal Hematopoiesis
- Quantitative Approaches to Study Cancer Evolution and Heterogeneity

#### Methods Workshops

**FRIDAY, MARCH 29**

- Controversies in Replication LCNA Measurements
- Defining Tumor Organ-systems with Single Cell Transcriptomics
- Game-Changing Technologies for High-Through-Put Functional Characterization of Cancer Gene Variants
- East Looks West: Chinese Pharma Explores Western Markets
- The Endothelium and Fluid Flows: Linking Metastasis and Immunity
- The Evolution of the Art and Science of Go/No Go Decisions in Cancer Drug Development
- Extracellular Vesicles and Intercellular Communication in Cancer
- Fibroblasts in the Driver’s Seat: Impact on Tumor Progression and Therapy Resistance
- Fluorescence Image-Guided Surgery for Improved Clinical Outcomes
- From Cancer Genomics to the 3D Organization of the Genome
- Functional Follow-Up of Microbiome Associations for Cancer Epidemiology Studies
- Impact of a Brexit on Oncology Drug Development and Regulation
- Making Your Voice Heard: How to Effectively Advocate for Cancer Research and Science-based Policy
- Metabolic Drivers of Cancer Molecular Regulation of Cancer Inflammation, Progression, and Treatment Resistance
- Obesity: The Effects of Local and Systemic Inflammation on Cancer
- Oncolytic Virus Therapy
- Ordering Genomic Changes as Actionable Targets in Pediatric Cancers
- Organoids as Model Systems in Cancer
- Pancreatic Tumor Microenvironment
- Personalized Circulating Tumor DNA Analysis for Familial Residual Disease Detection
- Precision Medicine in 2019
- Resistance to Therapies and Cancer Cell Dormancy
- Single-Cell and Spatial Genomics
- Stromal Niches for Organ-Tropic Metastasis
- Systems Biology Approaches to Cancer
- Targeting Cancer Neoantigens
- Tools for Machine Learning in Cancer Image Analysis
- Tumor Immunology and Immunotherapy for Nonimmunologists: Roundtable Discussions
- Tumor Immunology and Immunotherapy for Immunologists: Standard Cancer Therapies are Ultimately Immunotherapies
- Update on Young Women’s Breast Cancer
- Vascular-Immune Cell Cross-Talk: Implications for Cancer Immunotherapy
- West Looks East: Western Pharma Explores the China Mainland
Spotlight on Oncology

For more cancer research-related features and stories, visit our website at www.ddn-cancer.com

Cancer on the mind

Brain cancer is one of the more problematic malignancies in oncology, but research is progressing against its various forms, including glioblastoma multiforme and medulloblastoma.

Glioblastoma remains a difficult cancer to treat, but the brain malignancy is seeing increasing attention in R&D.

By Jeffrey Bouley

THERE ARE several cancers that pose particular challenges for treatment—and, by extension, for drug discovery and development—either because of their genetic makeup, because they are often discovered late, or other reasons. One of those “other” reasons, and one that often leads to late diagnosis for some of those cancers, is location. And location is a big problem when it comes to brain cancer, including glioblastoma multiforme (GBM), the most aggressive cancer that originates within the brain.

After all, not only do tumors in the part of your body that controls much of that body’s functions mean that GBM and other brain cancers can cause a host of problems aside from mortality, but the brain is a notoriously risky place to be conducting surgery or beaming radiation—and the blood-brain barrier makes it challenging to properly deliver drugs.

But recent years have seen a host of new research and development—and promising progress—against brain cancers, the subject that dominates this Spotlight on Oncology section. And, while GBM may be the brain cancer that gets the most attention, we will begin with medulloblastoma, the most common brain cancer among young children.

Florida State University (FSU), where researchers recently saw their medulloblastoma research published in the Journal of Cancer, says that the scientists on its campus are “making important progress in the battle against [this] class of devilishly complex human pediatric brain cancers.”

While there is no brain tumor more common than medulloblastoma among young children, there are no specific and effective therapies for this dangerous disease. As FSU notes, physicians have to resort to invasive and heavy-handed treatments like surgery, radiation and chemotherapy, often at the expense of the child’s quality of life.

Medulloblastoma, which is divided into four subgroups, is partially caused when a mutation occurs in the “driver genes” that either promote or suppress cancerous tumor growth—these mutations can be inherited, sporadic or environmentally induced. A team of FSU researchers, led by Dr. Qing-Xiang “Amy” Sang, a professor of chemistry and biochemistry, wanted to learn more about these mutations.

“Our unique Cancer Immunotherapy Array has already demonstrated its potential for the prediction of therapeutic response and immune-related adverse events in immuno-oncology. The extension into glioblastoma with a specific view to studying long-term survivors with one of the deadliest tumors provides a great opportunity to apply the array for the prediction of survival, but also to learn more about potential novel pathways for therapeutic intervention.”

Dr. Peter Schulz-Knappe, chief scientific officer of Protagen

Using data from the Catalogue of Somatic Mutations in Cancer, they identified a series of cancer-causing driver gene mutations and discovered that medulloblastoma is perhaps an even more dynamic and variable tumor than expected. “Most cancer is quite heterogeneous, but medulloblastoma is specifically very heterogeneous,” Sang said. “If you look at the driver gene mutation, it’s not as if the majority...
A viral approach to GBM

In other recent brain cancer R&D news, Mustang Bio Inc., a company focused on the development of novel immunotherapies based on proprietary chimeric antigen receptor engineered T cell (CAR-T) technology and gene therapies for rare diseases, and Nationwide Children’s Hospital announced Feb. 20 that they have partnered and entered into an exclusive worldwide license agreement to develop an oncolytic virus (C134) for the treatment of glioblastoma multiforme.

A Phase I clinical trial evaluating C134, an attenuated herpes simplex virus type 1 (HSV-1) intended for treating recurrent GBM, is being conducted at the University of Alabama at Birmingham (UAB). The trial is led by Dr. James Markert, chairman of the Department of Neurosurgery at UAB, who developed C134 in collaboration with Dr. Kevin Cassady, an associate professor of pediatrics at Nationwide Children’s Hospital. C134 is a second-generation HSV-1 oncolytic virus that has improved replication in tumors in mouse models of GBM, but with the same toxicity profile as its first-generation predecessors. In these preclinical studies, it reportedly not only demonstrated anti-tumor efficacy, but also resulted in regression of tumors that had relapsed following prior treatment with temozolomide.

According to FSU, while medulloblastoma’s heterogeneity makes it a challenging cancer to characterize and treat, this research will begin the process of helping scientists better identify opportunities for targeted, individualized treatments, by providing “a more comprehensive and nuanced understanding of which mutations happen where and when—and which mutations might defy broadly accepted definitions.”

Jack Robbins, who was an undergraduate when he co-authored the study, explained: “For medulloblastoma, a more personalized approach will have to happen. The goal we should be striving for is more MATCH-based trials in which we use molecular targets found from these different panels of driver events. These driver events extend past the genomic code and into epigenetic mechanisms that need to be further studied and assessed in the clinic to identify candidate therapies. We can hopefully give those therapies to patients who aren’t responding to the standard-of-care treatments.”

For those not familiar with it, NCI-MATCH, or MATCH, is a precision medicine cancer treatment clinical trial in which patients are assigned to receive treatment based on the genetic changes found in their tumors through genomic sequencing and other tests.

While the FSU researchers are proud of their findings, their work is only an initial step, with the next step in developing potential therapies being to develop credible laboratory models of human medulloblastoma tumor subgroups that can be used as evaluative tools in the search for potential therapeutics.

Cross-disciplinary collaborations may be a key to finding more effective therapies for this intractable disease. But another crucial key, Sang said, will be innovative ideas from a new generation of ambitious researchers. She remarked that this paper demonstrates the instrumental and field-defining contributions of student scientists.

**A viral approach to GBM**

For more information, visit www.DDN-News.com
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ted direct antitumor activity, but also elicited an immune response that can reverse tumor-associated immunosuppression.

The subsequent clinical trials are aimed at investigating a combination treatment of MB-101 (IL13Rα2-specific CAR) and C134. These trials, Mustang Bio says, are supported by preclinical studies that have appeared to demonstrate the synergic potential of an oncolytic virus, which can induce an antitumor immune response when combined with CAR-T therapy to target solid tumors.

“Oncolytic viruses often trigger an immune response directed at tumors that are otherwise refractory to single-agent immunotherapies. Our oncolytic virus C134 has demonstrated promising preclinical activity, and we look forward to working with Mustang to advance its development in the clinic,” Casady said.

Added Dr. Manuel Litchman, president and CEO of Mustang Bio: “We are very pleased to partner with Nationwide Children’s Hospital to develop oncolytic virus C134. We also plan to evaluate oncolytic virus C134 in combination with MB-101 to explore the potential synergies of this novel combination to treat patients with glioblastoma.”

**Consortium to study GBM survivors**

Toward the end of 2018, the European Organisation for Research and Treatment of Cancer (EORTC) and the Brain Tumor Center at University Hospital Zurich and chairman of the EORTC Brain Tumor Group. “However, we really need to understand the immunological profile and the immuno-competence of these patients better. Thus, investigating these patients by utilizing Protagen’s Cancer Immunotherapy Array may enable us to define their immune-profile, so that we can assess their immuno-competence. This will help us, together with the data already collected, to potentially understand why these patients survive for so long and how this can be extrapolated to other patients suffering from glioblastoma.”

“Our unique Cancer Immunotherapy Array has already demonstrated its potential for the prediction of therapeutic response and immune-related adverse events in immuno-oncology,” added Dr. Peter Schulz-Knappe, Protagen’s chief scientific officer.

“The extension into glioblastoma with a specific view to studying long-term survivors with one of the deadliest tumors provides a great opportunity to apply the array for the prediction of survival, but also to learn more about potential novel pathways for therapeutic intervention. Thus, we believe that applying our technology will result in a better understanding of the immunological profile of these long-term survivors, which will benefit all patients suffering from glioblastoma.

“We feel privileged that the EORTC Brain Tumor Group shares this vision, and are excited about the collaboration.”

**From the brain to the blood**

Concluding with a bit of a deviation and a twist, we have research out of the University of Texas MD Anderson Cancer Center from fall of last year that deals with brain infections rather than cancer—but while it is not a brain cancer they were researching, their findings might lead to future therapies that will help some patients suffering from blood-based cancers.

As MD Anderson notes, the emerging treatment known as adoptive T cell therapy has proven effective in a Phase 2 clinical trial for treating progressive multifocal leukoencephalopathy (PML), a rare and often fatal brain infection sometimes observed in patients with cancer and other diseases in which the immune system is compromised. The study, led by Dr. Katy Rezvani, a professor in the Department of Stem Cell Transplantation and Cellular Therapy at the University of Texas MD Anderson Cancer Center, reportedly showed marked improvement in three PML patients infused with donor T cells targeting the BK virus. Findings were published in the Oct. 11 online issue of the New England Journal of Medicine.

Results from the proof-of-principle study demonstrated BK, a virus similar to the JC virus which, although commonly found in the general population, can be deadly or cause serious health issues in some blood cancer patients, including those with leukemia and lymphoma. The virus is also a problem for people with AIDS, multiple sclerosis, rheumatoid arthritis, lupus and other autoimmune diseases treated with biologic therapies.

PML attacks white matter in the brain called the myelin sheath, which protects nerve cells. There is currently no effective treatment for PML, which is fatal in the majority of patients. Symptoms can include clumsiness or loss of coordination, difficulty walking, facial drooping, vision loss, personality changes, trouble speaking and weak muscles.

**EDITCONNECT: E031937**
A quick roundup of recent brain cancer clinical trial news

The National Brain Tumor Society (NBTS), a nonprofit dedicated to the brain tumor community in the United States, announced in January a partnership with the Global Coalition for Adaptive Research (GCAR), a nonprofit organization that it says brings together “some of the world’s foremost clinical, translational and basic science investigators.” As part of this partnership, NBTS has provided GCAR with a $750,000 award to help launch and build patient awareness of the world’s first global “adaptive” clinical trial for brain cancer, GBM AGILE (Glioblastoma Adaptive Global Innovative Learning Environment).

“The past decade of scientific advances has moved glioblastoma research to a pivotal point which calls for a platform like GBM AGILE to get potentially breakthrough medicines to patients—who can’t afford to wait—faster than standard clinical trial designs,” said David Arons, CEO of NBTS. “GBM AGILE is a ‘game-changer’ for neuro-oncology and is an opportunity for NBTS to collaborate with multiple stakeholders in the brain tumor field to revolutionize the future for patients. This trial also represents the spirit of the NBTS Defeat GBM Research Collaborative program, which was specifically designed to accelerate precision medicine research and take more ‘shots on goal’ by supporting opportunities to find treatments and a cure for the most deadly and aggressive type of brain tumor, glioblastoma.”

GBM AGILE is designed as a learning system to more efficiently and rapidly identify effective therapies for glioblastoma (GBM). GBM AGILE’s innovative model is designed to enable multiple drugs and combinations of drugs to be screened simultaneously and over time. Drugs that show initial evidence of benefit to patients will seamlessly transition to a confirmatory stage designed to support registration approval. Drugs that are underperforming are dropped. The intent is to lower the cost, time and number of patients required to evaluate potentially new effective therapies for patients with GBM.

“We are proud to partner with the National Brain Tumor Society, one of the most respected voices in the GBM community,” commented Dr. Brian Alexander, co-founder of GCAR. “As one of the original champions of GBM AGILE, we want to recognize NBTS’s early contributions to the trial design. GCAR is deeply grateful for their confidence, financial support to help launch the trial, and devotion and continued commitment to finding better treatments for this devastating disease.”

In late 2018, GCAR announced a partnership with Bayer Oncology to include the company’s drug regorafenib as the first therapy entering the GBM AGILE platform, a trial that was expected to begin early this year. Ultimately, the trial will include multiple arms at clinical sites throughout the United States, Canada and Australia, expanding into Europe and Asia in the near future.

GBM AGILE was first conceived in 2015 by an international group of more than 130 clinicians, researchers, biostatisticians, imagers, pathologists, patient advocates and leaders from government and industry. NBTS co-sponsored and participated in the early planning meetings, including co-chairing the original GBM Advocates Committee while the trial was still in its early development stages under the management

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The overall prognosis of glioblastoma patients remains poor, with median overall survival still in the range of only one year and long-term survival rare, but several companies are on the move with potential therapeutics against this cancer.

“We are very excited to study ibudilast with TMZ combination treatment as we believe ibudilast’s mechanisms of action and good penetration of the blood-brain barrier could benefit patients with recurrent GBM,” stated Dr. Patrick Y. Wen, principal investigator.

And, closing out our trial-related GBM roundup, late last year came news from VBI Vaccines Inc., a commercial-stage biopharmaceutical company developing next-generation infectious disease and immunooncology vaccines, that the independent data and safety monitoring board (DSMB) had completed its second safety assessment of the ongoing Phase I/II clinical study of VBI-1901 in recurrent GBM. The DSMB reviewed the complete safety data from the fully enrolled, intermediate-dose patient cohort, and unanimously recommended the continuation of the study without modification.

Following this recommendation, VBI initiated enrollment in the high-dose arm of the study. One final, pre-specified DSMB review is expected to occur after completion of enrollment in the high-dose cohort, concluding the dose-escalation phase of the study.

“We are encouraged by the sustained clean safety profile of VBI-1901 as concluded by this second DSMB assessment,” said Jeff Baxter, VBI’s president and CEO. “These positive safety reviews are critical milestones for the program and for patients diagnosed with this extremely aggressive tumor who currently have no effective treatment options.”

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

AI-driven GBM discovery

1ST Biotherapeutics and twoXAR form co-development collaboration

SEONGNAM, South Korea & MOUNTAIN VIEW, Calif.—1ST Biotherapeutics Inc., a preclinical-stage biotechnology company focused on neurodegenerative diseases, immunoncology and orphan diseases, and twoXAR Inc., an artificial intelligence (AI)-driven biopharmaceutical company, announced Jan. 3 an agreement to jointly discover and develop novel, efficacious treatments to address unmet medical needs in glioblastoma multiforme.

Under the agreement, twoXAR will use its proprietary AI technology to identify a set of drug candidates with the potential to slow, stop or reverse the progression of glioblastoma. twoXAR and 1ST Biotherapeutics will select candidates from this set to test in preclinical efficacy models of glioblastoma. Following identification of one or more candidates based on those evaluated, 1ST Biotherapeutics will use its team’s expertise in drug development to optimize candidates and finalize the creation of novel, efficacious treatments. Further details of the agreement were not disclosed.

“1ST Biotherapeutics is focused on efficiently building a pipeline of first-in-class therapeutic candidates with high likelihood of clinical success,” said Jamie Jae Eun Kim, CEO of 1ST Biotherapeutics. “The twoXAR team has a track record of rapidly identifying testable novel treatments that can lead to first-in-class therapeutics. This collaboration is an opportunity to combine twoXAR’s AI-driven drug discovery approach and the 1ST Biotherapeutics team’s expertise in chemistry and pharmacology to discover and develop effective molecular therapeutics for glioblastoma patients.”

“We are pleased to collaborate with 1ST Biotherapeutics, because we share common goals of efficiently discovering and developing novel therapeutics for diseases with high unmet medical need, such as glioblastoma,” added Andrew A. Radin, co-founder and CEO of twoXAR. “The 1ST Biotherapeutics team’s deep medical chemistry and drug development experience in CNS and oncology diseases provides a strong complement to twoXAR’s data-driven discovery approach.”

In other GBM trial news, CarThera, a French company that designs and develops innovative ultrasound-based medical devices to treat brain disorders, announced in January that it had secured approval from the French National Agency for Medicines and Health Products Safety (ANSM) to start a Phase 1b clinical trial of its SonoCloud-9 device in the treatment of recurrent glioblastoma.

The SonoCloud-9 (NCT 03744026) trial is an open-label, dose-escalation study to evaluate the safety and efficacy of temporaril

**CureVac secures new hire for preclinical development**

TÜRingen, Germany & BOSTON—Dr. Stefan Mueller has joined CureVac AG as its new vice president preclinical, the company announced last month. In this position, Mueller will manage CureVac’s preclinical programs from discovery to IND filing, and will be responsible for advancing the company’s pipeline. Most recently, Mueller served as global program leader for Ritasimab biosimilar at Sandz Biopharmaceuticals, and he has also held positions at Merck Serono, Merck and Knoll GmbH in the fields of toxicology, drug discovery and early drug development.

“It is an honor to join CureVac during this exciting time in the field of mRNA science,” Mueller commented in a statement. “CureVac is leading the way with its mRNA technology, and I look forward to utilizing it to better define preclinical product candidates that advance our mission to revolutionize human health through the unlimited possibilities of mRNA.”

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**Paving the way**

Shingles treatment the first of several herpesvirus drug candidates to enter IND-enabling studies

BY JIM CIRIGLIANO

SHELTON, Conn.—NanoViricides Inc., a technology platform-based company focused on treating viral diseases, has moved its first drug candidate into IND-enabling safety/toxicology studies, with plans to begin human clinical trials for a broad-spectrum drug candidate it hopes to develop for the treatment of herpesviruses.

The drug candidate NV-HHV-101 employed for these non-clinical IND-enabling studies is one of several compounds in development as candidates against VZV, the virus that causes chickenpox in children and shingles in adults. Upon successful completion of the safety/toxicology studies, NanoViricides expects to advance NV-HHV-101 into human clinical trials for a topical dermal treatment of the shingles rash as its initial indication.

**The data are in on CB 2679d-GT**

Catalyst Biosciences recently presented preclinical proof-of-concept data for its CB 2679d-GT factor IX gene therapy in hemophilia B mice.

BY MEL J. YEATES

SOUTH SAN FRANCISCO, Calif.—In early February, Catalyst Biosciences Inc. presented preclinical proof-of-concept data for its CB 2679d-GT factor IX gene therapy in hemophilia B mice. The adeno-associated virus (AAV)-based CB 2679d factor IX gene therapy candidate demonstrated superior results when compared with an AAV-encoded Padua vector in both reduction in bleeding times (fourfold reduction) and clotting activity (threefold improvement). The data were presented in a poster at the 12th Annual Congress of the European Association for Hemophilia and Allied Disorders (EAHAD) in Prague.

“These results are encouraging and demonstrate preclinical proof-of-concept for CB 2679d-GT, a gene therapy candidate encoding factor IX that we believe will be both superior to Padua and with a greatly reduced bleeding time reduction,” said Shawn Singh, CEO of VistaGen.

**Natural killer cells promise life**

GT Biopharma encouraged by clinical potential of triple-threat TriKe cells in cancer

BY KRISTEN SMITH

WASHINGTON, D.C.—Biotech newcomer GT Biopharma recently revealed promising results utilizing their proprietary Tri-specific Killer Cells (TriKe) to treat chronic myeloid leukemia (AML). Data presented at the American Society of Hematology (ASH) Annual Meeting demonstrate that their TriKe cells, when bolstered by the additional of the cytokine IL-15, show promising clinical potential for the treatment of AML, as well as myelodysplastic syndromes (MDS) and mastocytosis. The preclinical findings have resulted in FDA approval to conduct a first-in-human, first-in-class Phase 1 clinical trial, which will commence in the first half of this year.

GT Biopharma emerged in 2017 following a series of mergers and acquisition of Oxis International. The company has an exclusive partnership with Dr. Jeffrey Miller, deputy director of the University of Minnesota’s Masonic Cancer Center, in the ongoing refinement of the process. The relationship with Miller and his team offers what GT Biotech sees as a significant strategic advantage.

“We continue to be encouraged by the data from our TriKe program, [which is] being conducted by leading NK cell experts at the University of Minnesota. These findings have supported us with the confidence to proceed with our first-in-class TriKe Phase 1 study,” commented Dr. Raymond Urbanski, CEO of GT Biopharma.

“We are grateful to renowned NK cell expert, Jeffrey Miller ... and his team, and look forward to providing further updates as we continue to advance what we believe to be a potentially revolutionary product candidate.”

According to Miller, “These studies demonstrate the adaptability of the TriKe platform to optimize TriKe constructs and candidate selection.”
TRIKE CONTINUED FROM PAGE 35

in order to address unmet medi-
cal needs. We continue to work
with our partners at GT Biophar-
ma in moving the TriKE platform
forward.”

While T cell therapies have pro-
liferated over the last two decades,
their success as an immunotherapy
has been tempered by challenges
in refining dosing levels and in sig-
nificant instances of post-treatment
immunotoxicity for the patient. Miller
first identified natural killer (NK) cells
in 1994 as a means to engage one’s
own immune system to fight can-
cer, and has been working to refine
their use ever since. He understood
that NK cells would kill cells they
could identify as foreign, but, of
course, cancer is outstanding at
mimicking one’s own cells, thus
tricking the NK cells. By adding the
IL-2 cytokine, creating a bispecif-
ic killer cell, he was able to induce
activation of the NK cells, but can-
cer could still evade the immune
response. He continued with the
addition of IL-15, a cytokine that
induces cell proliferation, thus
making a TriKE. Lastly, the addition
of CD3 ensured that the specific
AML cancer cell was targeted and
killed by the NK cells.

“GT Biopharma utilizes the
NK stimulating cytokine human
IL-15 as a crosslinker between two
scFvs, which is designed to provide
a self-sustaining signal leading to
the proliferation and activation of
NK cells thus enhancing their abil-
ty to kill cancer cells mediated by
antibody-dependent cell-mediated
cytotoxicity (ADCC),” explains
Urbanski.

According to Urbanbski, once
the proof of concept is established in
the clinical trial, NK-based
technology could potentially be
programmed to attack any malignancy,
including solid tumors—moreover, NK-based
technology could possibly address numerous other diseases, like hematological disorders and autoimmune disorders like lupus and HIV.

“Shingles is not a lethal disease and
its incidence rate is once in a
lifetime for healthy persons, this
side effects profile may stand in
the way of substantial adoption
of this vaccine.”

Oral medications currently on
the market for treating shingles out-
breaks also leave room for improve-
ment, Diwan says.

“Available treatments for
shingles include oral antiviral
medications based on nucleotide
analogues (acyclovir, gancyclovir
and famciclovir). All of these
have poor effectiveness because,
unlike HSV-1 and HSV-2, the
virus that causes shingles does not
produce a good viral enzyme
called TK, which is required to
convert these drugs to active
forms,” he explains. “In addition,
very little of the orally taken drug
doesn’t get into the small site of
the infection, so the dosage of
diverse oral drugs for shingles
treatment is extremely high.
Additionally, they are effective
only if taken within the first 48
hours of the beginning of appear-
ance of the shingles rash—this is
almost always missed.”

“We anticipate that NV-
HHV-101 should be substantially
superior in viral load reduction
as well as in pain reduction
for the treatment of shingles; if
successful, this would mean
substantial superiority to exist-
ting treatments,” adds Diwan.

“Additionally, it is non-toxic
to the extent that we have been
to able to study it so far—the
IND-enabling safety/toxicology
studies have begun now. There-
fore, it can be applied as needed
to provide substantial relief of
symptoms, arresting the spread
of the rash, minimizing disease
pains and providing a supe-
rior quality of life. As a topical
cream with no evident adverse
effects, NV-HHV-101 should
enable strong patient compli-
ance as well.”

The progression of NV-
HHV-101 through IND-enabling
safety/toxicology studies and the
subsequent effort to move its
HSV-1 and HSV-2 treatments
into the development pipeline
are part of the company’s over-
all strategic goal of proving out
its technology platforms and
bringing antiviral treatments to
market.

“We are a technology plat-
form-based drug development
company, as our first drug proves
through the regulatory process,
it will prove that our postulates,
and mechanisms, are capable
of creating highly effective,
valuable drugs against viruses,”
says Diwan. “It will be a strong
validation with human proof of
principle. We have already dem-
strated proof of principle in
animal models against several
viral diseases.”

“The nanoviricide technol-
y has built in capabilities that
allow (i) attacking virus parti-
cles outside cells, (ii) attacking
virus replication in only virally
infected cells, sparing normal,
uninfected cells, as well as (iii)
eliminating latent viruses from
our customers’ skin, thereby
eliminating viral reactivation, thereby reduc-
ing pathology. Our next goal is to
additionally harness the part (ii)
capabilities, thereby providing a
complete cure for viruses that do
not have a latency phase. Once
these second-generation nano-
viricide drugs are developed, we
plan on engaging into the third
level of capabilities—that of
eliminating latent viruses from
the body, thereby curing as yet
incurable viral diseases includ-
ing herpesviruses … as well as
HIV/AIDS and a number of other
viral diseases.”

NanoViricides has moved its first drug candidate into IND-enabling
safety/toxicology studies as a topical dermal treatment of the shingles
rash for its initial indication.
Our engineered factor IX as a potential new treatment for hemophilia B,” said Dr. Nassim Usman, CEO of Catalyst. “The data indicate that CB 2679d-GT achieves a more rapid and robust hemostatic correction of bleeding in hemophilia B mice with a significantly improved clotting activity and four-fold reduction of bleeding time when compared with an AAV-encoding FIX-R338L Padua. We remain committed to advancing dalcinonacog alfa (Dalca — subcutaneous recombinant CB 2679d) into a Phase 2b study this quarter, and believe that CB 2679d-GT could be an important pipeline product that may provide additional treatment options for patients during their lifetime of therapy.”

According to Dr. Grant Blouse, vice president of translational research at Catalyst Biosciences, “CB 2679d-GT is a factor IX (FIX) adeno-associated virus (AAV)-based gene therapy construct using the same gene that is behind Catalyst’s high-potency, engineered recombinant FIX dalcinonacog alfa (Dalca) for the treatment of hemophilia B. Dalca is designed to improve three key functional attributes of FIX, and when given subcutaneously, Dalca has shown more than a 22-fold higher potency in early clinical studies compared with other FIX products on the market.”

“CB 2679d-GT encodes Catalyst’s high potency FIX variant that has three amino acid changes — R318Y/R338L/R343R. Current hemophilia gene therapy candidates encode the Padua or R338L variant,” Blouse continues. “The preclinical data demonstrate that CB 2679d-GT achieves a more rapid and robust hemostatic correction of bleeding in hemophilia B mice with significantly improved clotting activity and a four-fold reduction of bleeding time, when compared with an AAV-encoding FIX-R338L Padua.”

“These results are encouraging and demonstrate preclinical proof of concept for CB 2679d-GT, a gene therapy candidate encoding our engineered factor IX as a potential new treatment for hemophilia B.”

Dr. Nassim Usman, CEO of Catalyst

The 20-week preclinical study compared the activity of CB 2679d-GT with that of an AAV-encoding FIX-R338L Padua (FIX-Padua) in hemophilia B mice. Treatment with both CB 2679d-GT and FIX-Padua showed a reduced clotting time within the first week that remained stable up to the 20-week study endpoint. CB 2679d-GT demonstrated a statistically significant three-fold improvement in clotting activity (p < 0.04) compared to FIX-Padua. When evaluated at 20 weeks, there was a four-fold reduction in bleeding time after treatment with CB 2679d-GT compared to FIX-Padua at both the 5x10⁹ vg/mouse (p < 0.01) and the 1x10¹⁰ vg/mouse (p < 0.01) dose levels. These results suggest that CB 2679d-GT exhibits a superior hemostatic potency when compared with FIX-Padua.

“The FIX Padua variant is known to show increased activity compared with wildtype FIX, and in ongoing gene therapy trials treating individuals with hemophilia B it has demonstrated levels of FIX activity approaching the mild to normal range,” adds Blouse. “We are very encouraged and excited to see that when directly compared to an AAV-encoding FIX-R338L Padua in mice, treatment with CB 2679d-GT leads to significant additional improvements in reducing bleeding time and increasing clotting activity, thereby suggesting the possibility to provide a superior outcome.”

“We are currently focused on the continued development of our subcutaneous, recombinant Dalca product for the treatment of hemophilia B as well as our subcutaneous, recombinant Factor VIIIa candidate marzeptacog alfa (activated) being developed for the treatment of hemophilia A or B with inhibitors. We plan to explore co-development opportunities for CB 2679d-GT in 2020, and view CB 2679d-GT as an important pipeline product that may provide additional treatment options for patients during their lifetime of therapy. There is a need for the continued improvement of current hemophilia gene therapy constructs and vectors, so we believe CB 2679d-GT may become an important gene therapy candidate,” he concludes.
A collaborative effort by cosmetic company L’Oreal, biotech firm Hesperos Inc. (a researcher of which is pictured here) and the University of Central Florida is working to reduce the reliance on animal testing in drug and cosmetics development. The Hesperos system overcomes these limitations with a model that enables inter-action between its tiny organs, cultured in a serum-free blood surrogate solution from real human cells, in a way that realistically replicates system body responses to any compounds introduced to it and “confering a higher fidelity to predict human outcomes,” Hickman said. “Cells are all talking to each other. They are monitored with functional readouts without harming the cells.”

Hickman emphasized that this is important because the toxicity and efficacy of new compounds are studied upon both acute (single administration at high concentrations over a short-term period) and chronic (repeated or continuous administration at lower concentrations over an extended period) exposures. Whereas organ-on-a-chip models have previously been used for mechanisms of action validation (efficacy) and acute toxicity screening, they have not been suitable for long-term studies due to short half-lives, lack of organ-organ communication and outcomes that are difficult to extrapolate to human organ functions.

The Hesperos system overcomes these limitations with a model that enables inter-action between its tiny organs, cultured in a serum-free blood surrogate solution from real human cells, in a way that realistically replicates system body responses to any compounds introduced to it and “confering a higher fidelity to predict human outcomes,” according to the Advanced Functional Materials article. The system can also non-invasively monitor of cellular function is crucial in chronic toxicity testing as well as efficacy evaluation for drug registration at lower concentrations over a short-term period and chronic (repeated or continuous administration at lower concentrations over an extended period) exposures. Whereas organ-on-a-chip models have previously been used for mechanisms of action validation (efficacy) and acute toxicity screening, they have not been suitable for long-term studies due to short half-lives, lack of organ-organ communication and outcomes that are difficult to extrapolate to human organ functions.

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To be able to reach the 28-day testing milestone, Hesperos engineers used computational fluid dynamic modeling to mod-
Varlitinib falls short in gastric cancer

SINGAPORE—Recent news from ASLAN Pharmaceuticals featured a disappointing update on its Phase 2 clinical study, which evaluated varlitinib as a first-line therapy in HER1/HER2 co-expressing advanced or metastatic gastric cancer patients, and compared varlitinib plus mFOLFOX6 to placebo plus mFOLFOX6. Varlitinib is an oral small-molecule pan-HER inhibitor that targets EGFR receptors HER1, HER2 and HER4. The compound failed to meet the primary endpoint of significant reductions in tumor size following 12 weeks of treatment. Patients who received varlitinib plus mFOLFOX6 saw their tumors shrink an average of 22 percent after 12 weeks, compared to 12.5 percent for their tumors shrink an average of 22 percent following 12 weeks of treatment. Patients who received varlitinib plus mFOLFOX6 saw their tumors shrink an average of 22 percent after 12 weeks, compared to 12.5 percent for patients who received mFOLFOX6 alone, which was not statistically significant. The data did show that of the 17 cases of progression-free survival, there was tendency for an improvement in progression-free survival in patients treated with varlitinib.

MIXED RESULTS
Companies face both trial roadblocks and progress as they tackle DMD

BY ILENE SCHNEIDER
CAMBRIDGE, Mass. & LOS ANGELES—Duchenne muscular dystrophy (DMD), which is caused by mutations in the dystrophin gene, is progressive and irreversible, according to Ilan Ganot, co-founder, CEO and president of Solid Biosciences. Characterized by progressive muscle degeneration and weakness, the disease still lacks treatment options despite increased knowledge regarding its nature. In February, Solid Biosciences, a life-sciences company focused solely on finding meaningful therapies for Duchenne muscular dystrophy, announced preliminary findings from IGNITE DMD, its Phase 1/2 dose-ascending clinical trial to evaluate the safety and efficacy of SGT-001 microdystrophin gene transfer for DMD treatment. The company reported that initial three-month biopsy data showed low levels of microdystrophin protein expression, and said that it was engaging with “the appropriate parties.”

Nuzzyra fights pneumonia

Drug reportedly shown safe and effective in Phase 3 trials of adults with pneumonia and skin infections

BY MEL J. YEATES
BOSTON & MORRISTOWN, N.J.—In early February, Paratek Pharmaceuticals Inc. announced that The New England Journal of Medicine (NEJM) had published detailed results from the OPTIE D and OASIS-1 Phase 3 clinical trials of Nuzzyra (omadacycline). Both studies met all primary and secondary endpoints, and showed that Nuzzyra was safe and well tolerated.

Nuzzyra is specifically designed to overcome tetracycline resistance and exhibits activity across a spectrum of bacteria, including gram-positive, gram-negative, atypical and other drug-resistant strains.
“This study could change the way we treat patients with recurrent glioblastoma. One of the surprising aspects of this study was that most patients in the neoadjuvant group benefited, so it is unlikely that these results were due to chance.”

Dr. John de Groot of MD Anderson

“…benefited, so it is unlikely that these results were due to chance.”

As MD Anderson explains, cells generally rely heavily on two types of metabolism to survive. Mitochondria—oxidative phosphorylation (OXPHOS)—and the Warburg effect (glycolysis) are the two main routes. OXPHOS is a complex process that involves several enzymes and proteins in the mitochondrial membrane. The Warburg effect is a metabolic pathway that allows cells to rely on glycolysis for energy production, even in the presence of oxygen. This can be beneficial for cancer cells, as it allows them to grow and spread more quickly.

One of the surprising aspects of this study was that most patients in the neoadjuvant group benefited, so it is unlikely that these results were due to chance. The study included 35 patients with glioblastoma, a type of brain cancer that is one of the most aggressive and difficult to treat. The study protocol included the use of pembrolizumab, a PD-1 inhibitor, before surgery in the neoadjuvant group and before surgery or after surgery in the adjuvant group.

The researchers found that pembrolizumab was able to shrink tumors in patients with recurrent glioblastoma. This is significant because glioblastoma is one of the most aggressive cancers, and new treatments are urgently needed. The findings suggest that pembrolizumab could be a potential treatment option for patients with recurrent glioblastoma, and may provide new insights into the mechanisms of tumor growth and metastasis.

The study is expected to be completed in 2022, and the results will be presented at a future meeting of the American Society of Clinical Oncology (ASCO). The researchers are also planning to conduct a larger, randomized controlled trial to further evaluate the efficacy and safety of pembrolizumab in patients with recurrent glioblastoma.
positive, gram-negative, atypicals and other drug-resistant strains.

“[In both pneumonia and skin settings, Nuzyra’s] demonstrated efficacy against common pathogens, including pathogens resistant to other antibiotic classes, suggests that it has an important role for doctors in need of effective and safe IV and oral agents for their patients,” said Dr. Keith Kaye, director of research in the Division of Infectious Diseases at the University of Michigan Medical Center. OPTIC (Omadacycline for Pneumonia Treatment In the Community) was a global, pivotal Phase 3 clinical study that compared the safety and efficacy of once-daily IV-to-oral Nuzyra to IV-to-oral moxifloxacin for treating adults with CABP. OPTIC demonstrated that Nuzyra was non-inferior to moxifloxacin for the treatment of adults with CABP, and was safe and well tolerated. In the intent-to-treat population, Nuzyra (n=386) was non-inferior to moxifloxacin (n=388) for early clinical response (ECR) (81.1 percent vs. 82.7 percent), and investigator assessment of clinical response (IACR) at post-treatment evaluation (PTE) was 87.6 percent vs. 85.1 percent. Efficacy results were consistent across study populations, PORT Risk Class and causative pathogen.

The rate of serious treatment-emergent adverse events (TEAEs) was 6 percent in the Nuzyra-treated group and 6.7 percent in the moxifloxacin-treated group. The most common adverse events were gastrointestinal events (Nuzyra, 10.2 percent; moxifloxacin 18 percent) and included vomiting (2.6 percent vs. 5.4 percent) and diarrhea (1.5 percent vs. 8 percent), respectively. There were no cases of Clostridium difficile colitis or infection in patients treated with Nuzyra, compared with eight cases (2.1 percent) in patients treated with moxifloxacin. The mortality rate was 2.2 percent with Nuzyra and 5 percent with moxifloxacin.

“The publication of two of our global Phase 3 trials in a journal as prestigious as The New England Journal of Medicine is an affirmation of the clinical impact to the practice of medicine in an era of growing resistance to other antibiotic agents, and will help inform physicians’ decisions as they treat these serious, often life-threatening, community-acquired infections,” noted Dr. Evan Loh, president, chief medical officer and chief medical officer of Paratek. “These pivotal clinical trials demonstrated that Nuzyra is an effective, well-tolerated monotherapy option for patients with activity across an appropriate spectrum of bacteria, including gram-positive, gram-negative, atypicals and drug-resistant strains, and we believe Nuzyra can play an important role in winning the battle against the growing health challenge of antibiotic resistance,” says Dr. Evan Loh, president, chief operating officer and chief medical officer of Paratek.
“Our complementary ongoing AAT research programs in graft vs. host disease and organ preservation demonstrate the broad potential utility and scalability of our drug and its unique mechanism of action. We believe that this franchise of transplantation-related AAT treatments represents a significant market opportunity for Kamada.”

Amir London, CEO of Kamada

Positive data for TRC105

TRACON announces results from ongoing Phase 1b/2 trial in hepatocellular carcinoma

By DDNEWS STAFF

San Diego—TRACON Pharmaceuticals, a clinical stage biopharmaceutical company focused on the development and commercialization of novel targeted therapeutics for cancer, wet age-related macular degeneration and fibrotic diseases, in late January announced that positive clinical data from its ongoing Phase 1b/2 study of TRC105 and Nexavar (sorafenib) in patients with advanced hepatocellular carcinoma (HCC) were presented in a poster presentation at the ASCO 2019 Gastrointestinal Cancers Symposium in San Francisco.

Data from the ongoing open-label, non-randomized study were presented by Dr. Kanwal Raghav from the University of Texas MD Anderson Cancer Center. Key results included:

- Confirmed partial response by RECIST 1.1 occurred in 3 of 15 (20 percent) evaluable patients and a reduction of 50 percent or greater in alpha fetoprotein (AFP) concentration occurred in 8 of 16 (50 percent) evaluable patients.

- Reduction in AFP, a tumor marker expressed in patients with HCC, in early treatment may help predict a favorable response to treatment.

- Adverse events expected of each drug did not increase in frequency or severity when TRC105 and sorafenib were administered concurrently.

- TRC105 trough concentrations were lower in HCC patients compared with prior TRC105 studies in other tumor types, and weekly dosing at the recommended Phase 2 dose of TRC105 of 10 mg/kg, rather than every other week dosing, was required to exceed target concentrations consistently. This may reflect increased target mediated clearance in HCC patients via fibrotic/cirrhotic liver disease.

- Anti-drug antibody (ADA) was observed more frequently in patients with HCC (76 percent) compared with prior studies of TRC105 in other tumor types (e.g., in RCC, sarcoma, and lung cancer patients where ADA has been approximately 5 percent) and may have influenced pharmacokinetics in individual patients.

“We continue to be encouraged by the safety and activity of TRC105 in combination with Nexavar in patients with liver cancer,” said Dr. Charles Theuer, president and CEO of TRACON. “Importantly, the response rate from the current trial is superior to historic response rates reported from multiple trials of Nexavar as a single agent. We expect to complete enrollment of the current multicenter study by the end of this year, at which time we expect to correlate response with the soluble baseline biomarkers that are being collected as part of the study.”
DIAGNOSTICS

BRIEFS

‘Changing the face of genetic diagnostics’

Study shows Bionano’s Saphyr system accurately detects genetic disorder FSHD

BY LORI LESKO

SAN DIEGO—Bionano Genomics Inc., a life-sciences company that develops and markets Saphyr, a platform for ultra-sensitive detection in genome analysis, has released a journal article by scientists at China’s Wenzhou Medical University, Wenzhou Central Hospital, the First Hospital of Kunming and Berry Genomics that it thinks could “change the face of genetic diagnostics” in the future—even in the womb.

Using the Bionano Saphyr system to analyze patient samples, the researchers, writing in the journal Molecular Genetics and Genomic Medicine, obtained highly accurate molecular diagnoses of facioscapulohumeral muscular dystrophy (FSHD) in a multi-generation pedigree going back five generations in one family.

“This study is one of the most extensive in FSHD since we first began work in this disease with Johns Hopkins in 2017,” says Erik Holmlin, CEO of Bionano Genomics. “The comparison of Bionano genome mapping to existing methods such as Southern blot illustrates how Bionano Saphyr offers an improvement in workflow, while providing highly accurate results with the potential to increase clinical performance and utility by readily adding new clinical markers, such as the structural variation tied to a potentially milder form of FSHD described in this study, without modifying the assay or workflow.”

Although “DNA from amniocentesis has not been used on Saphyr, it is expected to be of sufficient quality for Bionano mapping—and could be used for a diagnosis of FSHD prior to birth,” Holmlin adds.

In the journal article entitled “Clinical application of single-molecule optical mapping to a multigeneration FSHD pedigree,” lead author Qian Zhang found that Saphyr was superior compared to the slow and cumbersome Southern blot current standard of testing. Plus, Saphyr has the potential to increase clinical performance by adding new clinical markers.

This enabled the team to identify the founder of the disease within the pedigree, as well as a variant of the FSHD1 region involving a duplication of one allele, Zhang says. Known as one of the most prevalent hereditary muscle diseases, FSHD is tied to variation in the size of DqZq arrays, in which a 3 kilo base pair unit on chromosome 4 is repeated multiple times. Southern blot is used to characterize array sizes above and below a threshold level today, but these workflows are slow and cumbersome and can

TAKING IT TO THE NOSE TO FIGHT LUNG CANCER

Veracyte announces strategic collaboration with Johnson & Johnson for development of nasal swab test

BY DDNEWS STAFF

SOUTH SAN FRANCISCO, Calif.—Veracyte Inc. announced in January that it had entered into a long-term strategic collaboration with Johnson & Johnson Innovation LLC and the Lung Cancer Initiative at Johnson & Johnson to advance the development and commercialization of novel diagnostic tests to detect lung cancer at its earliest stages, when the disease is most treatable.

The collaboration will build upon foundational “field of injury” science—where genomic changes associated with lung cancer can be identified with a simple brushing of a person’s airway—to develop new interventions that can save lives.

Under the terms of the agreement, Veracyte and the Lung Cancer Initiative at Johnson & Johnson, whose mission is to prevent, intercept and cure lung cancer, will combine clinical study cohorts involving more than 5,000 patients with multiple years of clinical outcome data. Veracyte will contribute bronchial and nasal samples from its clinical trials, which are part of the company’s extensive lung

PREDICTION PRECISION

New tool said to offer objective prostate cancer assessment

BY ILENNE SCHNEIDER

NEW YORK & LOS ANGELES—Prostate cancer, the third most common cause of death and the most prevalent male malignancy worldwide, is second to lung cancer in annual death tolls for American men. Although recent advances in prostate cancer research have saved many lives, objective prediction tools have been an unmet need.

Researchers from the Icahn PROSTATE CONTINUED ON PAGE 44

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Scientists at leading academic medical centers in China, together with commercial diagnostic laboratory Berry Genomics, used Bionano genome mapping to correctly characterize the molecular structure of the FSHD locus in the affected individuals of a five-generation pedigree.

The study determined that Bionano’s Saphyr system’s “moderate sample requirements and short time frame compared to Southern hybridization” — which, together with its “potential to identify structural variants such as deletions, duplications or rearrangements,” has shown it to be a better diagnostic tool, according to the researchers.

FSHD is a highly complex, progressive muscle-wasting disease commonly associated with weakening of facial, shoulder and upper arm muscles, sometimes robbing people of their ability to walk, talk, smile or even eat.

The progression often comes in bursts, with sudden deterioration followed by periods of no change. Despite being considered one of the most common forms of muscular dystrophy in adults and children, there are no treatments and no cure.

“FSHD is an autosomal dominant genetic disorder,” Holmlin explains. “It can develop spontaneously in an individual by deletion of part of the D4Z4 repeat array, such that the number of repeats is less than 10 copies on a 4qA ‘permissive’ allele.”

The estimated prevalence of FSHD is approximately one in 20,000 people, and it is estimated to affect about 750,000 individuals worldwide, he says.

“The goal of the studies that we are initiating involve the comparison of Bionano Saphyr data to current cytogenetic methods like FISH (fluorescent in-situ hybridization), karyotyping and aCGH,” Holmlin adds.

“There is great interest by the cytogenetics community to explore use of the Saphyr platform to modernize and potentially collapse the number of assays needed to interrogate samples required for testing. Furthermore, the combination of Bionano Saphyr and WGS (whole-genome sequencing) is being pursued as a discovery tool for identifying novel disease-associated structural variants in both oncology and genetic diseases — given that Bionano detects the structural variants missed by short-read NGS platforms.”

“The next step for Bionano Saphyr is to continue to streamline the workflow, improve sample throughput and further develop software analysis tools to enable rare variant detection in heterogeneous samples (e.g., cancer), and integrate our data with other ‘omics’ data sets through both internal R&D efforts and through external collaborations and partnerships.”

“The long-term goal for the Bionano Saphyr platform is to grow our global footprint of instrument placements in translational and clinical research, as well as cytogenetics and molecular pathology labs,” he concludes.

PROSTATE
CONTINUED FROM PAGE 43
School of Medicine at Mount Sinai have collaborated with researchers from the Keck School of Medicine at the University of Southern California (USC) to change that. The team has developed a machine-learning framework to precisely distinguish between low- and high-risk prostate cancer. Described in a Scientific Reports article, the framework is designed to help physicians, especially radiologists, to identify treatment choices for prostate cancer patients with less chance for unnecessary clinical intervention.

Standard methods to assess prostate cancer risk — multiparametric magnetic resonance imaging (mpMRI), which detects prostate lesions, and the Prostate Imaging Reporting and Data System, version 2 (PI-RADS v2), a five-point scoring system that classifies lesions found on the mpMRI — can predict the likelihood of clinically significant prostate cancer. Nonetheless, scoring is subjective and does not distinguish clearly between intermediate and malignant cancer levels, potentially resulting in different interpretations from clinicians.

By combining machine learning with radiomics (a branch of medicine using algorithms to extract large amounts of quantitative characteristics from medical images), the problem can be solved if enough machine-learning methods can be studied to address this limitation. The Mount Sinai and USC researchers developed a prescriptive framework to rigorously and systematically assess numerous methods to identify the best-performing one.

“The pathway to predicting prostate cancer progression with high accuracy is ever improving, and we believe our objective framework is a much-needed advancement.”

Dr. Gaurav Pandey of the Icahn School of Medicine

according to Dr. Gaurav Pandey, an assistant professor of genetics and genomic sciences at the Icahn School of Medicine at Mount Sinai and senior corresponding author of the publication, “By rigorously and systematically combining machine learning with radiomics, our goal is to provide radiologists and clinical personnel with a sound prediction tool that can potentially translate to more effective and personalized patient care.”

“The comparison of Bionano genome mapping to existing methods such as Southern blot illustrates how Bionano Saphyr offers an improvement in workflow, while providing highly accurate results with the potential to increase clinical performance and utility by readily adding new clinical markers,” says Erik Holmlin, CEO of Bionano Genomics. Leveraging more training and validation data sets than previous studies had. Thus, researchers could classify patients’ prostate cancer with high sensitivity and a high predictive value.

To conduct a comprehensive assessment of the candidate classifiers tested, the Precision-Recall F-measure family of evaluation measures was used in addition to the AUC score. This family is reportedly more informative about classifier performance in situations with unbalanced class distributions, typical in biomedical studies such as prostate cancer risk stratification, as it is true in this and other studies’ cohorts. The performance of the final classifier developed by the framework for assessing risk was evaluated in an independent cohort of prostate cancer patients, and compared to the PI-RADS v2 system to assess the relative utility of a well-developed combination of radiomics and machine learning for objective and accurate prostate cancer risk stratification.

Scientists at leading academic medical centers in China, together with commercial diagnostic laboratory Berry Genomics, used Bionano genome mapping to correctly characterize the molecular structure of the FSHD locus in the affected individuals of a five-generation pedigree.

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“By rigorously and systematically combining machine learning with radiomics, our goal is to provide radiologists and clinical personnel with a sound prediction tool that can potentially translate to more effective and personalized patient care,” says Dr. Gaurav Pandey, an assistant professor of genetics and genomic sciences at the Icahn School of Medicine at Mount Sinai. “Pictured here is the Mount Sinai Medical Center.

According to Dr. Gaurav Pandey, an assistant professor of genetics and genomic sciences at the Icahn School of Medicine at Mount Sinai and senior corresponding author of the publication, “By rigorously and systematically combining machine learning with radiomics, our goal is to provide radiologists and clinical personnel with a sound prediction tool that can eventually translate to more effective and personalized patient care. The pathway to predicting prostate cancer progression with high accuracy is ever improving, and we believe our objective framework is a much-needed advancement.”

Seventy-three prostate cancer patients with histopathologic diagnosis, mpMRI of the prostate and transrectal ultrasound-magnetic resonance (TRUS-MR) imaging fusion guided biopsy of the prostate within 2 months of mpMRI, diagnosed between March 2013 and May 2016, were included in the single-institution, retrospective study. Five patients were excluded, resulting in the final development set of 68 patients. The dominant lesion was chosen, and the patients were divided into high, intermediate and low categories per National Comprehensive Cancer Network guidelines. Then, these categories were combined into two classes — “high risk” and “lower risk” — to make the data fit into the traditional classification algorithms.

“To compensate for the substantial class imbalance in the development set — a higher number of lower-risk patients (54) than high-risk ones (14) — the researchers performed the classification algorithms constituting the framework with and without random oversampling. For all the algorithms, random oversampling provided improved performance across all the evaluation measures as compared to not oversampling.”
**From mice to man**

Elevated hormone flags liver problems related to methylmalonic acidemia

**BY DDNEWS STAFF**

BETHESDA, Md.—Researchers have discovered that a hormone, fibroblast growth factor 21 (FGF21), is extremely elevated in mice with liver disease that mimics the same condition in patients with methylmalonic acidemia (MMA), a serious genomic disorder.

Based on this finding, medical teams treating patients with MMA will be able to measure FGF21 levels to predict how severely patients’ livers are affected and when to refer patients for liver transplants. The findings also might shed light on more common disorders such as fatty liver disease, obesity and diabetes by uncovering similarities in how MMA and these disorders affect energy metabolism and the function of mitochondria.

The study was conducted by researchers at the National Human Genome Research Institute (NHGRI), part of the National Institutes of Health, and published Dec. 6 in JCI Insight.

“Findings from mouse studies usually take years to translate into healthcare treatment, but not in this case,” said Dr. Charles P. Venditti, senior author and a senior investigator in the NHGRI Medical Genomics and Metabolic Genetics Branch. “We can use this information today to ensure that patients with MMA are treated before they develop severe complications.”

The NHGRI team created a new mouse model and used it to discover key pathways that were affected during a fasting challenge to model a metabolic crisis in a patient with MMA. It enabled them to identify markers that they could then measure in MMA patients to assess the severity of the dysfunction in their mitochondria, specifically in the liver.

The NHGRI team will use FGF21 measurements along with other tests presented in the study in the design of upcoming gene-based clinical trials that the lab has worked on for many years. The NHGRI team will next assess the role of FGF21 pathways in other symptoms seen in MMA.

**SWAB**

Continued from page 43

Veracyte and Johnson & Johnson Innovation have teamed up for the creation of the first nasal swab test for early detection of lung cancer.

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UK’s Pathios signs CRO Sygnature

Deal focused on development of therapies in autoimmune disease and immuno-oncology

by Lori Lesko

Oxford, U.K.—Targeted toward developing first-in-class therapies for autoimmune diseases and immuno-oncology, biotech Pathios Therapeutics has joined hands with Nottingham, U.K.-based contract research organization (CRO) Sygnature Discovery to launch a partnership aimed at accelerating Pathios’ drug discovery and development programs.

The lynchpin of the collaboration hinges on Pathios’ integrated drug discovery program against a novel G protein-coupled receptor (GPCR) target and GPR65, a pH sensing GPCR. Signature is providing its expertise in GPCR bioscience and medicinal chemistry and deploying its computational chemistry, library design and screening capability to expand Pathios’ current hit-to-lead program.

Pathios says it brings together “cutting-edge European science” and its development team to modulate the activity of GPR65. This drug target is characteristic of certain T helper 17 (Th17) cell populations which have been shown to contribute significantly to the pathology of autoimmune conditions, such as ankylosing spondylitis and psoriatic arthritis.

“We founded Pathios in 2017 to build on emerging science that demonstrated GPR65 sits at the nexus of autoimmune disease and immunology, as this receptor links pathology caused by a low pH environment,” according to Tom McCarthy, executive chairman and co-founder of Pathios.

“The ultimate aim is to block the pathological process that GPR65 initiates without interfering with the physiological role of this receptor,” McCarthy says. “In addition, we aim to expand the therapeutic field for GPR65 to include Th17-related diseases and immuno-oncology, where our target has been shown to modulate the function of T cell populations.”

Pathios had formed an exclusive technology and marketing collaboration for sublingual delivery technology for sublingual and buccal delivery in the contract development and manufacturing organization sector.

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New year, new business

Protein-based therapies
Six.02 Bioservices launches

CONTRACT SERVICES

BRIEFS

New year, new business

London—Quanticate announced early this year that it had launched QVigilance as a dedicated pharmacovigilance (PV) and risk management business geared toward small and mid-size companies that are moving from clinical trials to post-marketing. Quanticate offers a variety of pharmacovigilance services, including case processing and reporting, global and local literature screening, aggregate production and reporting, signal and risk management, and regulatory intelligence and gate production and reporting.

“It is a natural progression for Quanticate to expand its capabilities through the launch of a company dedicated to delivering PV services,” said David Hukin, managing director of QVigilance. “It’s an area where we have always supported clients, and we have the expertise and experience required to contribute to their continued success.”

Sussection out a new alliance

Lausanne, Switzerland & Shanghai—AC Immune and WuXi Biologics have formed an exclusive technology and marketing collaboration for sublingual delivery technology for sublingual and buccal delivery in the contract development and manufacturing organization sector.

STA Pharmaceutical—a subsidiary of WuXi AppTec (pictured here)—has teamed up with BioLingus in the area of sublingual drug delivery, giving WuXi exclusive access to BioLingus technology for sublingual and buccal delivery in the contract development and manufacturing organization sector.

Under the tongue rather than getting the needle

WuXi STA and BioLingus sign technology and marketing collaboration for sublingual delivery

by DDNEWS STAFF

Shanghai & San Diego—Feb. 20 saw STA Pharmaceutical Co. Ltd. (WuXi STA)—a subsidiary of WuXi AppTec—and BioLingus, a Swiss biotech company, announce that they had formed an exclusive technology and marketing collaboration for sublingual delivery.

Under the terms of the collaboration, WuXi STA will have exclusive access to BioLingus technology for sublingual and buccal delivery in the contract development and manufacturing organization (CDMO) sector.

BioLingus has developed a novel platform to stabilize and deliver sublingually (orally under the tongue) drug targets—such as small molecules, peptides and proteins—that are currently administered to patients via injection. The collaboration will help further integrate the advantages of WuXi STA drug product services and expedite the development of BioLingus’ pipeline and usage of sublingual delivery technology.

In 2017, WuXi STA merged with WuXi Celltech to launch as “a new approach for providing bioservices to innovators pursuing protein-based research and product development.” Six.02 says it is bringing various specialty companies together under one management organization to deliver a coordinated continuum of best-in-class services that will enable protein-based innovators to optimize productivity and mitigate risk in their discovery, development and manufacturing programs.

“Protein production is notoriously difficult. Our goal is to create a more efficient and reliable contract services model for innovators tackling the challenges of protein-based research and product development,” said Michael Keefe, a partner at Six.02 Bioservices. “We’ve modeled Six.02 specifically to provide a new model for providing bioservices in protein-based R&D.”

Six.02 Bioservices launches

Company intends to be a ‘new model’ for providing bioservices in protein-based R&D

by DDNEWS STAFF

Rockville, Md.—In late January, Six.02 Bioservices announced its launch as “a new approach for providing bioservices to innovators pursuing protein-based research and product development.” Six.02 says it is bringing various specialty companies together under one management organization to deliver a coordinated continuum of best-in-class services that will enable protein-based innovators to optimize productivity and mitigate risk in their discovery, development and manufacturing programs.

“Protein production is notoriously complex. Our goal is to create a more efficient and reliable contract services model for innovators tackling the challenges of protein-based research and product development,” said Michael Keefe, a partner at Six.02 Bioservices. “We’ve modeled Six.02 specifically to provide a new model for providing bioservices in protein-based R&D.”
to developing potent and selective drugs to modulate GPR65, we are continuing to broaden the understanding of the fundamental biological processes that link to GPR65’s effects in Th17 cells, TAMs and other cell types.

“Our team has worked closely with Sygnature, and know they have the deep experience, expertise and drug discovery and development infrastructure to drive our program forward. I’m delighted that everyone is dedicated together and are committed to finding a cure for this rare condition. Sygnature also chose to invest in Pathios and expand our GPR65 drug discovery efforts, while we explore Series A funding opportunities from venture capital firms.”

McCarthy told DDNews. “Specifically, we have medicinal chemistry FTEs to build libraries around our current hit molecules and to identify new hit molecules in different chemical spaces. Sygnature is also providing bioscience resource to determine each molecule’s potency and selectivity in vitro. Finally, we are also taking a computational chemistry approach to drug GPR65.”

In the United States alone, 1.3 million people have been diagnosed with ankylosing spondylitis, while approximately 1 million people have been diagnosed with psoriatic arthritis, he adds.

Ankylosing spondylitis (AS) is similar to rheumatoid arthritis (RA) because in both diseases, people often report morning pain and stiffness and often feel feverish and fatigued and affected joints can feel swollen and tender. Some people with AS also experience eye symptoms, including redness, light sensitivity and blurred vision.

Psoriatic arthritis is a form of arthritis that affects some people who have psoriasis—a condition that features red patches of skin topped with silvery scales. Most people develop psoriasis first, and are later diagnosed with psoriatic arthritis, but the joint pain and swelling problems can sometimes begin before skin lesions appear, the Mayo Clinic reports.

No cure for the diseases exists, so the focus is on controlling symptoms and preventing damage to joints.

Recently published studies have demonstrated GPR65 drives tumor associated macrophages (TAMs) to adopt a phenotype that supports cancer immune evasion, McCarthy says, noting that he was influenced by Hussein Al-Mossawi, an Oxford-based rheumatologist who had identified that GPR65 was highly expressed in pathogenic Th17 cells in the blood and in synovial fluid from patients with two particular autoimmune diseases—ankylosing spondylitis and psoriatic arthritis.

Al-Mossawi showed these GPR65 expressing cells produced multiple cytokines that have been implicated in autoimmune disease, particularly IL17 and GM-CSF”, McCarthy reports. “Although he didn’t set out to identify GPR65, in hindsight there is a logical rationale for why this receptor might drive autoimmune disease as this GPCR signals in response to low pH, which characterizes an inflamed joint.”

Independently, Aviv Regev’s group at the Broad Institute also showed that GPR65 drives Th17 mediated autoimmune disease in a mouse model, and together with GM-CSF are amongst the most highly expressed genes in pathogenic T cells, he adds. Modulating GPR65 offers the potential to treat autoimmune disease by reducing multiple cytokines that are triggered by the low pH environment of an inflamed joint. The other pathology characterized by a low extracellular pH is cancer.

While it has been known for several decades that tumors exist in an acidified microenvironment due to metabolic changes, a 2018 publication from Tobias Bopp’s group in Mainz, Germany showed that low pH signaling through GPR65 polarized tumor associated macrophages to adopt a phenotype that supports immune evasion.

The goal of this collaboration “is to identify potent and selective GPR65 modulators and demonstrate initially in vitro, and eventually in vivo, proof of concept—i.e. that modulation of GPR65 with a small molecule impacts the level of multiple cytokines triggered in a low pH environment,” according to McCarthy.

“We want to take a GPR65 modulator into the clinic and demonstrate it delivers a best-in-class and first-in-class treatment for autoimmune disease without significant immune suppression,” he explains. “In parallel, we will hopefully show that this same mechanism of action will prevent tumor immune evasion.”

Simon Hirist, CEO of Sygnature, says, “We are extremely pleased to take this exceptional opportunity to partner with, and invest in, Pathios on their drug discovery projects. Based on our diligence activities, we are excited about the potential for GPR65 modulation to be central to new treatments for autoimmune disease and a critical mechanism of action in next-generation immuno-oncology drugs targeting the tumor microenvironment.”

“We are excited to have the opportunity to work with Tom and the rest of Pathios’ tremendously talented team again and contribute to the potential positive impact their therapeutics will have on patients’ lives.”

“We entered into this exclusive collaboration with WuXi STA for this technology in the CDMO sector for a number of reasons. Principally, WuXi STA is one of the world leaders in this field, with an integrated CMC platform from preclinical development to commercialization. Furthermore, this partnership will help us develop our own client base on a global scale faster and more broadly than we could do on our own,” said Yves Decadt, CEO of BioLingus.

Added Dr. Min Zhang, Chief Karnataka, CEO of WuXi STA: “We are very pleased to partner with BioLingus and to offer their award-winning sublingual delivery technology to global new drug developers via WuXi STA’s integrated CMC platform. This collaboration will therefore offer more economical, convenient and effective delivery solutions for patients globally.”
Targets acquired

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

BY JEFFREY BOULEY

HERE’ S ALREADY been some awfully significant activity in this year in terms of merger and acquisition (M&A) deals, and we haven’t even gotten past March yet. Just last week, we discussed the Bristol-Myers Squibb (BMS) agreement to pay $74 billion for Celgene, and an $8 billion deal for Eli Lilly and Co. to acquire Loxo Oncology.

And now there are three more deals with big names involved: GE Life Sciences, Roche Group and Merck & Co. Let’s start with GE, because even though it’s “only” a bit under a third the size of the BMS-Celgene deal, that’s still a lot of money.

Feb. 25 saw news that Danaher Corp. had entered into a definitive agreement with General Electric Company (GE) to acquire the Biopharma division of GE Life Sciences for a cash purchase price of approximately $21.4 billion.

GE Biopharma is a leading provider of tools, consumables and software that support the research, discovery, process development and manufacturing workflows of biopharmaceutical drugs. The business is comprised of process chromatography hardware and consumables, cell culture media, single-use technologies, development instrumentation/consumables and service. GE Biopharma is expected to generate annual revenue of approximately $3.2 billion in 2019, with approximately 75 percent of these revenues considered recurring.

The business will be established as a standalone operating company within Danaher’s $6.5 billion Life Sciences segment, joining

Novartis exercises option to license AKCEA-APO(a)-LRx

Phase 3 planning and initiation activities underway; Akcea earns $150-million license fee

BY DDNEWS STAFF

BOSTON & CARLSBAD, Calif.— Akcea Therapeutics Inc., an affiliate of Ionis Pharmaceuticals Inc., announced Feb. 25 that Novartis has exercised its option to license AKCEA-APO(a)-LRx, a drug to treat patients with elevated levels of lipoprotein(a), or Lp(a), and established cardiovascular disease (CVD). AKCEA-APO(a)-LRx, referred to by Novartis as TQ1290, was discovered by Ionis and co-developed by Akcea and Ionis. Akcea will receive a $300 million license fee that will be split equally with Ionis.

Elevated Lp(a) is an independent genetic risk factor for CVD that cannot be managed by lifestyle modifications, including diet or exercise, or with treatment using existing cholesterol-lowering therapies. It is estimated that there are more than eight million patients living with CVD and elevated levels of Lp(a).

“We are very pleased that Novartis, an established global leader in drug development and commercialization, will now shepherd this landmark therapy through late-stage clinical development and toward the market,” said Paula Soteropoulos, CEO of Akcea. “The Phase 2 study results presented last year at AHA showed that AKCEA-APO(a)-LRx significantly reduced Lp(a) levels below the recognized threshold for cardiovascular risk in patients living with cardiovascular disease, and elevated

Merck & Co. plans to add immunotherapy company Immune Design to its ranks, at the price of $300 million.

BY JEFFREY BOULEY

HERCULES, Calif.— Leading off the latest round of the deals of the pharma and biotech industry is the acquisition (M&A) news this week. Considerable activity in the biotechnologies, technology and software and biopharma sectors was evident this week, as the biotech news landscape continues to shift. This week, the new breed of biotech companies was on display with guided selection methods displayed at the AHA (American Heart Association) meeting.

The new range of recombinant monoclonal anti-idiotypic antibodies is comprised of four inhibitory anti-bodies that are highly specific for the humanized IgG2a/kappa monoclonal antibody drug, eculizumab, a biotherapeutic that is used to treat paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome.

The anti-eculizumab inhibitory antibodies can be used to quantify the level of eculizumab in patient samples, and they may also be used in bioanalytical assays for biosimilar development. An antibody pair is suitable for the development of a pharmacokinetic (PK) bridging ELISA, and antibodies of high, medium and low affinity can be used as a positive control or calibrator in an anti-drug antibody assay.

The recombinant monoclonal anti-idiotypic antibodies are generated using the Human Combinatorial Antibody Library (HuCAL) and Cys-Display, a proprietary method of phage display with guided selection methods to obtain highly targeted reagents.
the company’s Pall, Beckman Coulter Life Sciences, SCIEX, Leica Microsystems, Molecular Devices, Phenomenex and IDT businesses.

“GE Biopharma is renowned for providing best-in-class bioprocessing technologies and solutions. This acquisition will bring a talented and passionate team as well as a highly innovative, industry-leading product suite to our Life Sciences portfolio, providing an excellent complement to our current biologics workflow solutions,” said Danaher’s president and CEO, Thomas P. Joyce Jr. “We expect GE Biopharma to advance our growth and innovation strategy in an important and highly attractive life-sciences market. We see meaningful opportunities to harness the power of the Danaher Business System to further provide GE Biopharma’s customers with end-to-end bioprocessing solutions that help enable breakthrough development and production capabilities.”

The transaction is expected to be completed in the fourth quarter of calendar year 2019.

Spark Therapeutics set to join Roche
PHILADELPHIA—The same day of the Danaher-GE M&A news brought word that Spark Therapeutics, a fully integrated, commercial gene therapy company dedicated to “challenging the inevitability of genetic disease,” had entered into a definitive merger agreement for Roche to fully acquire it at a price of $114.50 per share in an all-cash transaction. This corresponds to a total equity value of approximately $4.8 billion on a fully diluted basis, inclusive of approximately $500 million of projected net cash expected at close. The merger agreement has been unanimously approved by the boards of both Spark and Roche.

Under the terms of the merger agreement, Roche will promptly commence a tender offer to acquire all outstanding shares of Spark’s common stock, and Spark will file a recommendation statement containing the unanimous recommendation of the Spark board that Spark shareholders tender their shares to Roche.

“As the only biotechnology company that has successfully commercialized a gene therapy for a genetic disease in the U.S., we have built unmatched competencies in the discovery, development and delivery of genetic medicines. But the needs of patients and families living with genetic diseases are immediate and vast,” remarked Jeffrey D. Marrazzo, CEO of Spark Therapeutics. “With its worldwide reach and extensive resources, Roche will help us accelerate the development of more gene therapies for more patients for more diseases and further expedite our vision of a world where no life is limited by genetic disease.”

Spark Therapeutics’ proven expertise in the entire gene therapy value chain may offer important new opportunities for the treatment of serious diseases,” added Severin Schwan, CEO of Roche. “In particular, Spark’s hemophilia A program could become a new therapeutic option for people living with this disease. We are also excited to continue the investments in Spark’s broad product portfolio and commitment to Philadelphia as a center of excellence.”

Spark Therapeutics will continue its operations in Philadelphia as an independent company within the Roche Group.

Merck to acquire Immune Design
KENILWORTH, N.J., SEATTLE & SOUTH SAN FRANCISCO, Calif.—Merck, through a subsidiary, had entered into a definitive M&A agreement for Merck to acquire Immune Design. “We believe this agreement creates shareholder value by positioning our company’s proprietary technologies, GLAAS and ZVes, are engineered to activate the immune system’s natural ability to generate and/or expand antigen-specific cytotoxic immune cells to fight cancer and other chronic diseases.”

“Merck has a rich history of discovery and innovation and a strong track record of developing meaningful therapeutics and vaccines,” stated Dr. Carlos Paya, president and CEO of Immune Design. “We believe this agreement creates shareholder value by positioning our company’s technologies and capabilities for long-term success with a leading, research-driven biopharmaceutical company.”

The transaction is expected to close early in the second quarter of 2019.

The Phase 2 study results presented last year at AHA showed that AKCEA-APO(a)-LRx significantly reduced Lp(a) levels below the recognized threshold for cardiovascular risk.”

Paula Sotereopoulos, CEO of Akcea

Akcea-APO(a)-LRx is an antisense drug developed based on Ionis’ proprietary Ligand Conjugated Antisense, or LICA, technology platform. Ionis’ proprietary LICA technology platform has the potential to produce new drugs that can be used at lower doses and with less-frequent administration compared to non-LICA antisense drugs. AKCEA-APO(a)-LRx is designed to inhibit production of apolipoprotein(a), or Apo(a) protein, thereby reducing systemic levels of Lp(a).
COMMENTARY: FDA draft guidance on in-vitro DDI studies

How will it impact your drug discovery program?

By Dr. Ron Laethem of BioIVT

The U.S. Food and Drug Administration (FDA) published a new in-vitro drug-drug interaction (DDI) guidance on October 25, 2017, entitled “In Vitro Metabolism and Transporter Mediated Drug-Drug Interaction Studies: Guidance for Industry.” This was the first new DDI guidance on the FDA’s current thinking since February 2012 when it released “Drug Interaction Studies—Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations.” It was long-anticipated and didn’t disappoint those who like change. There is a lot to take in from this latest guidance, and some significant changes were presented. As with all guidelines in this area, the FDA does not establish legally enforceable responsibilities, but rather presents recommendations that reflect the mindset of those who will be reviewing your regulatory filings. Ignore this valuable insight at your peril.

Along with many tactical changes suggested in the guidance, there were a couple of strategic changes as well. One overarching theme was the further acceptance and promotion of modeling and simulation to more fully assess DDI risk before entering the clinic. When in-vitro DDI studies are carried out appropriately, the data can be used to make in-vivo predictions of potentially clinically relevant DDIs. This insight is invaluable for designing appropriate clinical studies to prevent missteps and potentially avoid having to repeat trials.

“As with all guidelines in this area, the FDA does not establish legally enforceable responsibilities, but rather presents recommendations that reflect the mindset of those who will be reviewing your regulatory filings. Ignore this valuable insight at your peril. Along with the many tactical changes suggested in the guidance, there were a couple of strategic changes as well. One overarching theme was the further acceptance and promotion of modeling and simulation to more fully assess DDI risk before entering the clinic.”

Another major strategic shift was the endorsement of moving in-vitro metabolic studies to earlier in the drug development continuum, prior to first-in-human (FIH) studies. This concept isn’t new, and the intense pressure for pharmaceutical companies to reduce the high attrition rates in discovery has led to the deployment of drug metabolism and pharmacokinetics (DMPK) assays earlier in the development process. Assays such as metabolic stability, cytochrome P450 (CYP) inhibition and nuclear receptor reporter assays have been steadily moving closer to the discovery arena. This shift has resulted in better-quality drug candidates from an absorption, distribution, metabolism, and elimination (ADME) standpoint, but attrition rates are still very high in the pharmaceutical industry.

The major driver for FDA desiring to shift the in-vitro assays earlier in development is so that the data can be used to better design clinical trials and prevent the unnecessary exclusion of subjects. This rationale was stated in the FDA’s clinical DDI guidance that was released in tandem with the in-vitro DDI guidance (Clinical Drug Interaction Studies – Study Design, Data Analysis, and Clinical Implications). Patients in randomized controlled trials are, by definition, random; however, this can lead to studies where the volunteers are unrepresentative of the reference population for which the drug is to be prescribed.

By studying DDIs for a drug candidate more fully, it should be possible to better recruit for a trial and not exclude representative participants based solely on the fact that they are taking one or more other medications. Reducing this selection bias should enable improved studies where the data more accurately represent the target population for whom the intervention is intended. This paradigm, in theory, should also provide the FDA with data that will allow it to better assess the risk and benefits of an investigational new drug to the intended patient population.

While this approach should lead to better outcomes for the pharmaceutical industry and patients, it does require some changes to be made with respect to the drug development process. Currently, definitive in-vitro metabolic studies aren’t carried out until later in development, often after FIH clinical studies. This is because DDIs aren’t normally a concern for FIH studies when healthy volunteers with no concomitants are recruited. The advantage of this paradigm is that the clinical Cmax for the experimental drug is known and can be used to guide the design of the definitive in-vitro metabolic studies and ensure that the results are relevant to the in-vivo situation. The FDA in-vitro DDI guidance suggests that when using high concentrations of test article in cellular systems, such as hepatocytes for CYP induction or mammalian cell lines for transporter studies, cytotoxicity can become limiting. If the highest achievable concentration of the test article is outside the realm of physiological relevance, the cytotoxicity can confound results and raise concerns that may not be relevant in vivo.

When designing the in-vitro metabolic studies, the sponsor will have animal PK data to guide the concentration ranges used in vitro, and indeed this is a major part of determining the doses for FIH studies. However, the quality of the human dose prediction varies significantly for different potential drugs and having the clinical Cmax value is of great help in designing in-vitro studies that give predictive data. It would be taking a step backward for sponsors to run definitive in-vitro studies using nonclinical data to guide in-vitro study design, only to have to repeat those studies after clinical FIH data is available that suggests those original concentrations are not clinically relevant.

Using the highest solubility concentration of test article in vitro addresses the clinical relevance issue for assays that don’t involve cellular systems, such as inhibition studies using pooled human liver microsomes. If the concentration range goes low enough from the highest solubility concentration, the data should cover all the possible Cmax concentrations that will be determined in the FIH studies. However, as noted above, for the cellular systems this could be problematic.

Using high concentrations of test article with the in-vitro cellular systems, such as human hepatocytes, could take an approach similar to the microsomal work. Rather than employing the limit of solubility as the benchmark, acceptable cytotoxicity would dictate the highest concentration used. However, the interplay between the cytotoxicity and the assay readout must be defined. For instance, in a CYP induction study using cultured human hepatocytes, how do we know if the cytotoxicity is relevant to the in-vivo situation? One approach is to determine the highest tolerated dose with the cultures and then use this to inform the concentration at that dose.

This assumes that the dose-limiting cytotoxicity is reflective of what happens in vivo. If the cytotoxicity is an artifact of the in-vitro system, the study may not be able to reach concentrations that are found in the FIH studies to be clinically relevant. This would necessitate having to do a clinical study to look at the inductive potential.

If we implement in-vitro metabolic assays prior to FIH studies, greater care must be given to the concentrations of test article used. This is particularly important for cell-based assays where cytotoxicity can confound results. For in-vitro assays using cells, particularly human hepatocytes, we must ensure that the test system is accurately recapitulating all of the biological processes relevant to the in-vivo situation. For hepatocytes, this means that in addition to metabolic capacity and properly functioning nuclear receptor signaling pathways, the cultures should also maintain robust uptake and efflux transporter function. Setting up and deploying appropriate test systems to handle higher, and potentially non-physiological, concentrations of test article will be key to avoiding doing in-vitro assays both before and after FIH studies.

Sandwich-culture systems using hepatocytes that have physiologically relevant uptake and efflux function, appropriate regulatory function and are metabolically-competent have been shown to have better in vitro/in vivo extrapolation (IVIVE) correlations than monolayer models. The improved predictability of the sandwich-culture system is likely due to the model being better able to manage high concentrations of test article and recapitulate how the liver is able to respond to a drug.”

Ron Laethem, Ph.D., is lead, in vitro research at BioIVT, Hepatic Research Services
Bio-Rad’s new range of recombinant monoclonal anti-idiotypic antibodies is comprised of four inhibitory antibodies that are highly specific for the humanized IgG2/4 kappa monoclonal antibody drug, eculizumab, a biotherapeutic that is used to treat paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome.

**EDGE CONTINUED FROM PAGE 49**

The recombinant production method also ensures a consistent and secure supply.

“Bio-Rad’s portfolio of highly specific anti-biotherapeutic antibodies continues to expand, providing critical reagents for use in preclinical and clinical development of biosimilars, and for therapeutic drug monitoring of patients,” said Amanda Turner, Bio-Rad’s product manager for the Life Science Group.

“Our unique anti-eculizumab antibodies are well characterized and have been validated for use in PK and immunogenicity assays. Adding new specificities to our portfolio will help researchers overcome challenges associated with assay design and sensitivity,” she added.

The anti-eculizumab antibodies are approved for in-vitro research and for commercial applications of in-vitro testing services that support preclinical and clinical drug and biosimilar development and patient monitoring.

More efficient and easier lab management

SOMERSET, N.J.—Also in early February, LabVantage Solutions, a global provider of laboratory informatics solutions and services, unveiled LabVantage 8.4, the latest version of the company’s comprehensive laboratory information management solution. Encompassing LIMS, ELN and LES, LabVantage 8.4 incorporates new and updated features that increase lab efficiency and effectiveness while making the work of managers and staff easier. The most significant changes include new features for work planning and managing resource capacity and availability, as well as enhanced capabilities to ensure data privacy.

“LabVantage 8.4 includes many valuable new features, but we are most excited by its unprecedented work assignment and resource planning functionality—the most powerful and robust available today,” noted John Heiser, CEO of LabVantage Solutions. “We understand that managing resources, workflow and staff is one of our customers’ biggest challenges. Our new Work Assignment and Resource Planning (WAP) module greatly simplifies and facilitates this process, empowering our users to manage their laboratories and workflows more efficiently and effectively with far less time and hassle. With LabVantage 8.4, laboratory directors can finally optimize the use of their operations for their individual labs or network of labs.”

New and updated features of LabVantage 8.4 include work assignment and resource planning, data privacy, a new master data navigator, bulk data import and automated issue tracking and submission.

**The Andrew Alliance Pipette+ system “uniquely provides both full traceability and improved repeatability in manual pipetting for life-sciences laboratories.”**

*Software-enabled pipettes*

GÖTTINGEN, Germany & GENEVA—A pair of companies announced recently the launch of the Andrew Alliance Pipette+ system, which they say “uniquely provides both full traceability and improved repeatability in manual pipetting for life-sciences laboratories.”

This product alliance to bring an “intelligent pipetting solution” to market pulls together Andrew Alliance S.A., a robotics company with an innovative approach to liquid handling that is improving repeatability of conventional laboratory pipettes, and the life-sciences company Sartorius.

The partners state that as much as half of all research funding in life sciences is used to repeat experiments, “showing that lack of reproducibility in research is an ongoing challenge in the biopharmaceutical industry. A major cause of irreproducibility has been incorrect execution in liquid handling workflows. This collaboration between Andrew Alliance and Sartorius reflects both common methodologies, the new assays reportedly have no cross-reactivity with other flaviviruses, including Dengue, West Nile, yellow fever, Japanese encephalitis, tick-borne encephalitis and Usuto virus.

“The Native Antigen Company Zika Virus NS1 ELISA assay is a highly sensitive and specific assay suitable for the quantitative detection of Zika Virus NS1 in a range of biological samples, with no cross-reactivity with other flaviviruses. Present in human serum during the early stages of infection, the NS1 protein provides an early marker of viral replication following infection. This ELISA assay can detect NS1 antigen at levels as low as 5 pg/ml and enables researchers to measure the level of Zika NS1 protein in infected patients, offering value in epidemiology studies.”

In an independent assessment of the Zika Virus IgG/IgM/IgA ELISA kit, external researchers reported a sensitivity of 90.3 percent and specificity of 92.1 percent. This compared favourably with direct testing and is reported to be highly sensitive and specific for Zika virus detection and monitoring, which to date has always been hampered by Zika’s cross-reactivity with dengue,” said Dr. Andy Lane, commercial director at The Native Antigen Company. “The impact of this exciting development will be seen across academia, public health and the pharmaceutical industry.”

In addition to the kits, The Native Antigen Company also offers an extensive range of Zika virus antigens, both expressed as recombinant proteins in a mammalian expression system and as native viral preparations. Further products include NS1 proteins (from both the prototypic Uganda strain and from the Suriname strain responsible for the major outbreak in 2016) and Zika virus-like particles.

**High precision in endpoint detection**

WALKERSVILLE, Md. & BASEL, Switzerland—Lonza recently unveiled PytoTec PRO, said to be the first-ever fully automated, plate-based robotic solution for endotoxin detection. Integrated with the latest version of Lonza’s proprietary dynamic control WinQKCL 6.0 Software platform, the new system has been designed to meet the needs of rapidly changing requirements of quality control testing laboratories for fully automated processing of simple to complex sample matrices.

As a powerful combination of robotic liquid-handling technology with an automation software module, the system reportedly:

- Improves data integrity organically with the capture of new metadata from the automated preparation, adding traceability into tracking, trending and audit controls
- Can take any new and existing templates and dynamically “script” the instructions to an automation template with relatively minimal effort from the end user, regardless of how complex the sample type or testing requirements
- Enhances assay robustness and reproducibility for increased confidence in the accuracy and precision of results
- Significantly reduces manual intervention, simplifying QC testing workflows and eliminating the human error potential
- Reduces re-test rates, as well as out-of-specification and out-of-trend deviations, thereby improving the laboratory’s performance
- Integrates with laboratory information management systems or Lonza’s MODA Solution, facilitating fully paperless workflows and traceability of sample lifecycle
- Offers considerable cost savings compared with conventional cartridge-based systems, which require the use of expensive reagents
- Aligns with the U.S. Food and Drug Administration’s Process Analytical Technology Initiative and Data Integrity requirements and is fully compliant with the U.S. Pharmacopoeia Bacterial Endotoxin guidelines

“The introduction of the PytoTec PRO Automated Robotic Solution and WinQKCL 6.0 Software marks a milestone in endotoxin detection, allowing pharmaceutical manufacturers to replace manual, error-prone processes with a fully automated solution,” commented Robert Porzio, product manager for endotoxin detection at Lonza. ✩
Focus Feature: Artificial Intelligence

AI gives hope to patients and researchers

Artificial intelligence cannot solve every problem, but it has the potential to break up many bottlenecks

BY JEFFREY BOULEY

HERE IS A LOT OF HOPE bottled up in life-sciences examinations and pharma/biotech research and development. Hope for insight, novel breakthroughs and new discoveries—and yes, hope for profit as well. And for the patients who look for therapeutic help against myriad conditions and diseases, as well as for the healthcare professionals who treat them, hope for significant relief and, better yet, outright cures.

Human ingenuity has gotten us far over the centuries in terms of medicines. Technology now gives us more than we can handle with our minds, particularly with voluminous genomic (and other omics) datasets and sometimes millions of leads to follow up. And that, of course, is where artificial intelligence (AI) is potentially a very great boon to life-sciences and therapeutic R&D.

Insilico Medicine, which focuses on artificial intelligence for drug discovery, biomarker development and aging research, is one of the many entities looking to capitalize on the hope of AI. One way it is doing that is with a research collaboration agreement announced last year with A2A Pharmaceuticals Inc., a biotechnology company headquartered in New York and focused on development of novel drugs for unmet needs in oncology, drug resistant bacterial infections and other life-threatening diseases.

What the two companies have done is create a fledgling company—Consortium.AI—that will be tasked with applying the latest advances in AI to discovery of novel small molecules for rare and orphan disease, with a focus in particular at first on Duchenne muscular dystrophy (DMD).

As Insilico notes, computationally pre-optimized new drug candidates have already been designed for targets validated through its AI system. For its part, A2A Pharmaceuticals will assume the management of the new company, provide the development expertise for the newly discovered compounds and will serve as the contact point for any licensing of compounds.

“We are pleased to partner with Insilico Medicine, combining our strengths and complementary technologies to accelerate development of better therapeutics into the clinic for the patients that need them,” said Dr. Elena Diez Cecilia, head of business development at A2A. “Muscular dystrophy is a debilitating and terminal degenerative condition that causes muscle inflammation and wasting, and there is a huge need for more effective therapies.”

Both companies will collaborate on research programs devoted to the development of therapeutic approaches for DMD and other severe genetic disorders. Insilico Medicine’s technology applies advances in deep neural networks to identifying critical disease targets and generation of novel chemistry using next-generation artificial intelligence. A2A uses proprietary computational tools, including artificial intelligence, to design highly selective therapeutics for difficult-to-drug targets like protein-protein interactions.

“A2A Pharmaceuticals has a team of highly talented drug hunters with a proven track record in discovery, development and licensing of the drug candidates... This is fantastic application for AI,” said Alex Zhab-rokov, founder and CEO of Insilico Medicine.

Head games for AI

On the not-so-rare disease side, Dr. Iya Khalil, co-founder and chief commercial officer of GNS Healthcare, talked recently on the company’s blog about another area of unmet—or at least incompletely met—need: migraines.

There are existing treatments for migraines and new ones that have come down the pipeline in recent years, but as Khalil points out, no one has been able to pin down the exact biological causes of migraines. There is a widely held belief is that the disease is a neurobiological disorder—an illness of the nervous system that’s caused by biological factors like genetics and metabolism.

Treatment options right now are generally twofold: pain-relieving medications and preventive medications. The FDA recently approved a drug that helps prevent migraines by targeting a protein called CGRP.

“Two obstacles stand in the way of progress however. First, the potential demand for new treatments may far outpace the supply of new drugs,” wrote Khalil. “The potential market for these drugs could be much larger than anticipated, as migraine often goes undiagnosed. Some reports estimate that 60 percent of women and 70 percent of men suffering from the condition have never been diagnosed with migraines.” The second challenge could come from insurance companies that might be hesitant to approve reimbursement, especially for expensive new preventative medications.

“Forunately, more pharma companies are now leveraging AI and machine learning to help overcome these obstacles. This is particularly important as companies grapple with forecasting demand for newly developed therapies,” Khalil added. “Causal machine learning, a powerful form of AI, is poised to make a real impact in areas like migraine, where there is still much to understand about the disease. By developing causal disease models, biopharma is better able to analyze clinical trial results and extract value from data that often is inconclusive or riddled with confounding factors. These models can identify which patients respond to treatment and explain the crucial cause-and-effect relationships within the data. The result is often the identification of biomarkers for those patients who benefit in relation to the population as a whole.”

Speeding up the pipeline process

To even get to the point of clinical trials, however, you not only have to discover promising candidates, but optimize them and turn them into actual medications that can be...
AI-driven discovery company closes Series B round

OSFORD, U.K.—Excisentia, an artificial intelligence (AI)-driven drug discovery company, announced in January it had raised £6.7 million in a Series B financing round, which will be used to scale the company’s pipeline and advance selected programs toward clinical development.

One of the new investors is Colin Green, and as noted by Dr. Rupert Vessey, president of research and early development there: “Excisentia has demonstrated that AI in molecular design is here today. With the global pharmaceutical industry acknowledging the importance of incorporating AI-driven R&D approaches into their drug discovery processes, we see a huge growth opportunity ahead. We believe Excisentia is set to become a global leader in AI-driven drug discovery and are excited to participate in this investment.”

Excisentia has made what it calls “considerable progress during 2018” and anticipates its first programs driven by AI will be IND-ready by early 2020, if not before.

“This Series B marks a milestone in our development and enables us to drive the next phase of strong business growth. Over the past 12 months we have substantially expanded our operations and capabilities to become a full stack AI drug discovery company,” said Prof. Andrew Hopkins, CEO and founder of Excisentia. “Furthermore, our unique Centaur Chemist platform allows us to move rapidly from idea generation to new drug molecules ready for IND and clinical development. With this new funding Excisentia is positioned to become the dominant player in AI drug discovery, driving radical change in R&D productivity. We are excited Celgene and GT Healthcare have joined with existing investor Evotec on this exciting journey.”

Add Dr. Werner Lanthaler, CEO of Evotec: “We continue to be very impressed with the progress Excisentia has made over the past year. Through our partnership with Excisentia, we have seen first-hand evidence that they can deliver the most productive drug discovery engine in the industry. This latest funding will allow Excisentia to apply its platform at scale, taking advantage of the efficiencies that its AI-driven systems provide.”

AI for ‘sparse’ data

HELSINKI, Finland—Normally, we think of using AI for huge and complex data sets, but drug-enabling nanotechnology company Nanoform aims to enhance its proprietary STARMAP nanonization technology by applying “sparse data AI.”

To that end, the company has announced Prof. Jukka Corander as head of artificial intelligence.

Corander is a world-leading expert in AI, Nanoform says, employing state-of-the-art machine learning techniques to create simulation-based models from sparse data. He is currently professor of biostatistics at the University of Oslo in Norway and professor of statistics at the University of Helsinki in Finland. His recent work with the Wellcome Sanger Institute Cambridge, U.K., includes the application of statistical machine learning and Bayesian inference algorithms on biological data. Corander will apply his expertise to further develop Nanoform’s STARMAP. The implementation of AI will help define the physical characteristics of drug candidate molecules from limited data to understand how these parameters influence solubility and bioavailability.

Sparse data AI will combine with Nanoform’s best-in-class technology for nanonization success for new drug candidates and form a more efficient particle engineering process for drug development. The software will also be used to enhance Nanoform’s nanofabrication process by implementing deep learning for consistent, iterative improvement.

Nanoform’s appointment of a head of AI is, the company says, in response to the significant interest in AI for drug discovery, as “AI can be used to model alternative applications of current drug compounds and determine how particle engineering can produce optimal drug design and formulation. Nanoform’s partners are set to benefit from this innovative approach to drug discovery and development, which significantly increases the likelihood of identifying successful compounds that can quickly progress to market.”

“My partnership with Nanoform provides an exciting opportunity to fully realize the power of sparse AI technologies in the pharmaceutical industry ... we will be able to transform the way that drug candidates are discovered, developed and manufactured,” says Prof. Jukka Corander, Nanoform’s new head of AI.
Phase 1 data indicate potential of mRNA encoding VEGF-A as a regenerative therapeutic

CAMBRIDGE, Mass.—Moderna Inc., a clinical-stage biotechnology company pioneering messenger RNA (mRNA) therapeutics and vaccines to create “a new generation of transformative medicines for patients,” announced Feb. 20 the publication of a Phase 1α/b study in Nature Communications showing the potential of mRNA encoding for vascular endothelial growth factor A (VEGF-A) as a regenerative therapeutic. This approach aims to stimulate the growth of new blood vessels, also known as angiogenesis, to improve blood flow in tissues where it is otherwise restricted.

The Phase 1α/b study, conducted with AstraZeneca, was a randomized, double-blind, placebo-controlled study in Europe of men with type 2 diabetes mellitus. The VEGF-A mRNA was delivered in a saline solution and was administered by intradermal injection into forearm skin in single ascending doses. The trial met its primary objectives of describing safety and tolerability and secondary objectives of protein production and changes in local blood flow post-injection.

“I believe this is an important milestone in the field of mRNA therapeutics as it starts to address many questions regarding the safety and delivery of mRNA to human tissues, the duration and level of the protein that can be expressed, and the ability of the technology to have a physiologic, measurable function over a prolonged period of time,” said Dr. Kenneth Chien, a professor in the Department of Cell and Molecular Biology and the Integrative Cardio Metabolic Center at the Karolinska Institute in Stockholm, a Moderna scientific co-founder and co-author on the paper. “Based on these early data, this approach may provide benefit to patients where proper blood flow is compromised in areas such as heart disease and diabetes, as well as for other vascular complications.”

The study showed VEGF-A protein post-injection of AZD8601 was increased above the pre-specified expected threshold, as measured by skin microdialysis. At each sampling time, mean VEGFA protein levels across all mRNA-treated sites from patients across all cohorts, were higher than that of placebo up to the 24- to 26-hour time point in the study. The bioactivity of the VEGF-A protein post-injection of AZD8601 was also observed by an increase in blood flow at injection sites up to seven days following a single injection, as measured by laser doppler imaging. The only treatment-related adverse events reported were mild injection-site reactions, and the treatment was overall well tolerated.

“We are encouraged by these initial data as they support the ability of AZD8601 to transiently produce pharmacologically active amounts of VEGF-A protein, which may in the future regenerate blood vessels for patients with ischemic cardiovascular disease,” said Dr. Tal Zaks, chief medical officer at Moderna. “These findings improve our understanding of the potential for Moderna’s mRNA to produce therapeutic levels of protein and help patients with a wide range of serious diseases.”

UTRECHT, Netherlands—Sapreme Technologies, a biotech company developing a technology platform to enable the cytosolic delivery of macromolecule therapeutics, announced in February that it had been awarded a €6.6 million grant together with a multidisciplinary consortium that includes 11 other academic and industrial parties. The grant was provided by the European Union (EU) through Horizon 2020 to support the development of a non-viral-based gene therapy using Sapreme’s proprietary endosomal escape enhancers.

Sapreme was founded in 2016 and develops new technologies in the field of macromolecule therapeutics, such as antibody-drug conjugates (ADCs) and oligonucleotide-based therapeutics for cancer and other diseases. Endolysosomal trapping is a major hurdle in drug target engagement for oligonucleotide-based therapeutics and a number of ADCs. Sapreme has a proprietary technology called ENDOSCOPE that improves escape of macromolecule therapeutics from endolysosomes.

“Sapreme to help develop oligonucleotide delivery platform

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“We are pleased to see that the EU has recognized the great potential of the ENDOSCOPE project and the expert multi-disciplinary consortium developing a novel oligonucleotide delivery technology for treatment of cancer and hemophilia patients,” said Ruben Postel, chief scientific officer of Sapreme. Added Ernst Geutjes, acting managing director: “The fact that the EU awarded the proposal with the maximum score demonstrates the potential of Sapreme’s proprietary endosomal escape enhancement technology, as well as the exceptional quality of the proposal and the [ENDOSCOPE] consortium spearheaded by Sapreme and Charité-Universitätsmedizin in Berlin.”

Sapreme to help develop oligonucleotide delivery platform
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