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**RNA to repair a heart**

Scripps team identifies molecule that can bind to RNA to increase VEGF-A production

**BY KRISTEN SMITH**

JUPITER, Fla.—Dr. Matthew Disney, a research chemist and professor in the Department of Chemistry at the Scripps Research Institute’s Florida campus, began his career looking to defy skeptics. The structure and shape of human RNA fed the belief that it was essentially undruggable, but a drive to unlock the capability drove Disney from the inception of his work as a scientist.

And now that RNA focus might help fix broken hearts.

The Human Genome Project indicated that we produce more RNA than proteins and that non-coding RNAs were driving healthy and disease biology. Disney’s prolonged deep exploration of the three-dimensional structure of RNA found deep pockets there, and our upcoming new website and redesigned magazine!

The unique capability of ADAR to potentially correct these mutations creates significant opportunities for us to hopefully treat a broad spectrum of human diseases, including diseases that currently have no treatments or only sub-optimal treatments,” says Dr. Chandra Vargese, chief technology officer for Wave.

In a recent webcast, Wave relayed updated RNA editing data from other companies and researchers that we are aware of showed low levels of editing (at most, low single-digit percentages). The only other published scientific paper where ADAR editing was used showed a percentage of percentages in editing,” Dr. Chandra Vargese, chief technology officer for Wave, tells DDN. “In our non-human primate (NHP) proof-of-concept study, we saw up to 50 percent A to I (G) editing of ACTB mRNA in the liver of NHPs two days after the last dose. So, we are excited that we are one of the leaders in this emerging field.”

“To date, in-vivo RNA editing data from other companies and researchers that we are aware of showed low levels of editing (at most, low single-digit percentages). The only other published scientific paper where endogenous ADAR was used showed a percentage of percentages in editing,” Dr. Chandra Vargese, chief technology officer for Wave, tells DDN. “In our non-human primate (NHP) proof-of-concept study, we saw up to 50 percent A to I (G) editing of ACTB mRNA in the liver of NHPs two days after the last dose. So, we are excited that we are one of the leaders in this emerging field.”

Wave Life Sciences releases preclinical data for ADAR editing and C9orf72 program

**BY KELSEY KAUSTINEN**

CAMBRIDGE, Mass.—While genomic editing and CRISPR are all the rage in the industry of late, Wave Life Sciences is focusing its efforts on the RNA side of things, and the company’s efforts are being rewarded with encouraging preclinical data.

Wave’s novel RNA-editing platform uses endogenous ADAR (adenosine deaminases acting on RNA) enzymes via free uptake of A-to-I base editing oligonucleotides, also known as ADAR editing. Unlike with DNA editing, the effects of RNA editing are reversible, which avoids the potential damage of permanent off-target DNA editing. The free uptake of this platform means that the approach requires no viral vectors or nanoparticle delivery, simplifying the process.

In May, Wave reported the successful RNA editing of ACTB (beta-actin) mRNA in non-human primates via endogenous ADARs through using stereoregular GalNAc-conjugated oligonucleotides. In a proof-of-concept study, these oligonucleotides achieved up to 50 percent A-to-I (G) editing of ACTB mRNA in the livers of primates, and recent durability data showed significant editing even 45 days after the last dose—with the implication that the editing could last even longer.

“Riding The Wave”

Wave Life Sciences has successfully conducted RNA editing in neurons within several tissue types in a humanized mouse model, including the cortex, hippocampus, striatum, brain stem, cerebellum and spinal cord.

At the late-stage end of the preclinical phase is Wave’s C9orf72 variant-selective silencing program in amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). The candidate in question, WVE-004, targets C9orf72 by selectively silencing the V1 and V3 transcripts and sparing healthy C9orf27 protein. Genetic mutations in C9orf72 are the most common genetic cause of the familial forms of ALS and FTD, and these mutations also play a role in sporadic forms of each disease.

In a recent webcast, Wave relayed updated preclinical data for the C9orf72 program. In a BAC transgenic mouse, Wave saw sustained knockdown of up to six months of expanded C9orf72 repeat transcripts and dipeptide repeats in the spinal cord and cortex after two intracerebroventricular doses. The company is planning to submit a clinical trial application to explore WVE-004 in ALS and FTD in a proof-of-concept trial in the fourth quarter of this year.
ONCOLOGY REMAINS MARKET-LEADING THERAPY

GlobalData shows this area with $142B in sales for 2019, continuing strong growth trend

LONDON—In a global prescription drug market worth over $600 billion in sales, oncology has become the dominant area, claiming a market share of 23.4 percent as of 2019—followed by immunology at 12.4 percent and metabolic disorders at 10.8 percent—according to data and analytics company GlobalData.

GlobalData’s analysis of a proprietary dataset shows that global drug sales with oncology as their key therapy area reached $142 billion in 2019, having sustained a compound annual growth rate (CAGR) of 15.4 percent since 2000.

“Oncology drug sales growth has been extremely impressive, increasing from 7.6 percent to 23.4 percent over 20 years,” said Dr. Sakis Paliouras, an oncology analyst at GlobalData. “While immunology and genetic disorders have sustained the highest CAGRs over 20 years at 18.5 percent and 18.3 percent, respectively, oncology seems to operate on a different scale, having sales that nearly doubled since 2013 and being the only therapy area to ever cross the $100 billion-per-year mark.”

Oncology drug sales started rising above other therapy areas after 2015 and have continued increasing at a steep pace. Other disease areas seem to have reach plateaus, with cardiovascular and respiratory indications having seen no growth after 2011.

According to GlobalData, a larger number of available drugs does not explain this difference, as infectious diseases and metabolic disorders have significantly more drugs available than oncology, but far fewer total sales. GlobalData attributes the sales gap to a combination of a higher number of blockbuster drugs in oncology and a higher number of new market entrants in oncology since 2015.

Concludes Paliouras: “There has never been a more exciting time in oncology, with years of research and development efforts now being rewarded with great commercial success. Furthermore, a large number of oncology indications remain underserved, highlighting an opportunity for continuous clinical research that will result in the value of this market exploding further.”

In other oncology market news from GlobalData, the company has noted that as novel immuno-oncology (IO) drugs become established in the market, a new trend of combinatorial treatments is arising, explaining, “The race to develop combinatorial drugs is increasing, with more companies including IO potentiating drugs in their pipelines and investigating these in combination with established IO drugs.”

“While immunology and genetic disorders have sustained the highest CAGRs over 20 years at 18.5 percent and 18.3 percent, respectively, oncology seems to operate on a different scale.”

Dr. Sakis Paliouras, an analyst at GlobalData

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Miguel Ferreira, an analyst at GlobalData
COVID-19 accelerates momentum nationwide for life-sciences real estate demand

CHICAGO—Rankings of the top U.S. life-sciences cluster hubs were released recently in the “JLL 2020 U.S. Life Sciences Outlook,” which also tracks the progress of up-and-coming life-sciences markets that are fast becoming options of choice for companies and investors alike. Emerging hubs are looking to real estate to boost productivity as they anticipate growth of the worldwide prescription drug market, expected to surpass $1 trillion by 2022.

Boston, San Francisco and San Diego retained their rankings as leaders among U.S. life-sciences ecosystems and top contenders for venture capital investment, capturing 70 percent of all venture capital (VC) investment in 2019. Boston and San Francisco also lead the other clusters significantly with respect to development, with 2.7 million square feet and 4 million square feet under construction, respectively.

New York, Los Angeles and Philadelphia increased their cluster scores since 2019, reaching new peaks in VC funding and life-sciences employment. As speed to market accelerates for many pharmaceuticals, proximity to incubators at major research institutions has also supported developing clusters such as Raleigh-Durham, Houston and Maryland, which have attracted recent interest from developers such as ARE, Longfellow and Hines.

“Conditions are ideal for maximum profitability arising from innovative new pharmaceuticals and medical devices. Meaningful advances within the life-sciences industry, such as machine learning, are creating new sources of workflow and thus real estate demand.”

Audrey Symes, research director for JLL Healthcare and Life Sciences

Additionally, the race for development of COVID-19-related vaccines is already beginning to energize demand in pharma-heavy New Jersey, a trend that should spread to more markets as 2020 progresses, according to professional services firm JLL.

“Each cluster has a different specialty and occupies its own point along the maturity spectrum, providing a diverse range of options for investors and occupiers alike,” said Roger Humphrey, executive managing director of JLL Life Sciences. “But they do share a major commonality. Each cluster features a highly educated workforce and ties to the research community, which in turn attracts a steady stream of multi-sourced investment that creates a need for institutional real estate.”

Beyond COVID-19’s recent acceleration of innovation in the life-sciences industry, life-enhancing pharmaceuticals and medical devices have been increasingly sought out by millennials reaching the peak of their earning potential and seeking personalized experiences, JLL noted. The upcoming expiration of a suite of patents creates an opportunity for mid-tier life-sciences companies to pursue new long-term profit sources. Many new products on the market and in development are curative rather than therapeutic, increasing marketing potential and overall category growth.

“Conditions are ideal for maximum profitability arising from innovative new pharmaceuticals and medical devices,” said Audrey Symes, research director for JLL Healthcare and Life Sciences. “Meaningful advances within the life-sciences industry, such as machine learning, are creating new sources of workflow and thus real estate demand. This combination of simulative factors sets up the life-sciences industry to expand at an unprecedented pace, both in terms of manufacturing and patient demand.”
**Lodo Therapeutics acquires Conifer Point**

**Innovative approach for modulating cellular metabolism could treat a variety of diseases**

**Good news on COVID-19 front**

**Jnana and Roche investigate SLCs**
improved analogues can enter infected cells and stop the virus. Further preclinical studies will then be necessary, including those involving animal models. Although we are excited about the results, we still have a long way to go.”

Nowick explained that the UCI-1 macrocycle was synthesized by Fmoc-based solid-phase peptide synthesis, followed by cyclization in solution phase, deprotection and purification by HPLC. He added, “UCI-1 is designed to bind to the active site of the SARS-CoV-2 main protease enzyme through non-covalent interactions. This approach is a different from a number of other inhibitors that have been reported, which rely on covalent bond formation to the active site cysteine of the protease.”

The next steps are to get an X-ray crystallographic structure that will further guide the structure-based drug design process and allow the design of inhibitors with improved activity and other properties, and to determine whether UCI-1 and improved analogues can enter cells and block the replication of the virus. “Once we have an analogue with good activity in cells, we will be ready to test the compounds in an animal model,” Nowick remarked.

“We believe that improved homologues will have commercial potential. For this reason, we have filed a provisional patent application that encompasses UCI-1 and its analogues,” he reported. “I could envision drugs that come from this work, as well as the efforts of others, leading to treatments for COVID-19. I could also envision prophylactic preventions, akin to PrEP as a prevention for HIV/AIDS. Had these efforts been done back in the SARS outbreak of 2003, or perhaps the MERS outbreak in 2012, we might have had a drug in hand to fight the current pandemic. There will likely be additional coronavirus pandemics in the future that will benefit from the current drug development efforts against COVID-19.”

“We next need to improve the inhibitor to achieve stronger inhibition. We also need to test whether the molecule and improved analogues can enter infected cells and stop the virus ... Although we are excited about the results, we still have a long way to go.”

Dr. James Nowick of the University of California, Irvine

Nowick and his team named the macrocycle University of California, Irvine Coronavirus Inhibitor-1, or UCI-1, to indicate that it is the first molecule in what will still be a long journey to create a drug to treat or prevent COVID-19. Now that Nowick’s lab has a prototype called an “initial hit,” researchers need to make additional molecules that are more effective in blocking the protease. Then they must figure out how to actually deliver the best molecule to infected cells. This means that while the new macrocycle is a promising first step, Nowick stated that, “People need to understand that it’s a long way from a drug candidate.”

“The identification of an initial hit is only a first step toward the identification of a drug candidate,” he continued. “We next need to improve the inhibitor to achieve stronger inhibition. We also need to test whether the molecule and improved analogues can enter infected cells and stop the virus.”

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small molecules that bind to those pockets. While RNA had generally been thought to be undruggable, these binding small molecules presented a world of possibility.

In a new study conducted at Scripps Research Institute, Disney illustrates how that can be applied in response to specific disease molecules to help repair heart tissue damaged by heart attacks and heart disease with medication. With his team, he unlocked a pathway to restart a factor called VEGF-A, short for vascular endothelial growth factor A, that is known to improve blood flow and stimulate stem cells to rebuild blood vessels and muscle following a heart attack. VEGF-A is known to be suppressed in diseased hearts, hindering organ repair, but the Disney team found a solution.

Over time, Disney and Scripps developed an informatics database of small molecules known to bind with RNA. AstraZeneca approached the lab and challenged them to utilize Scripps’s database in conjunction with theirs to find a binder that would stimulate message RNA to create a key therapy to repair damaged heart tissue, specifically aiming for one that would increase VEGF. In several rounds of cross-computational models using computational and experimental models, they found a microRNA precursor called pre-miR-377 that acts like a dimmer switch for VEGF-A production in failing heart muscle. In fact, the search of the two databases increased the dataset of RNA binders by 20-fold.

“We could drug RNA by knowing which genes were dysregulated in a failing heart,” Disney explains. “We wanted to short-circuit that dysregulation to have a downstream pathway of increasing VEGF to repair the damage. Some RNAs will be overproduced to silence VEGF; if you can re-increase it, you can repair that damage. During a heart attack, the injury causes proteins that could promote new, healthy blood vessel growth to go silent. We analyzed the entire pathway for how the protein is silenced, and then we used that information to identify how to reinvigorate its expression.”

Their exploration found numerous hits to the target, while recognizing that there were “on” targets and “off” targets, and the team engineered a hybrid molecule that achieved a remarkable on-target specificity. While the compound has not yet been tested in animals, Scripps is seeking funding for the next steps, even with the likelihood that AstraZeneca and other pharmaceutical companies may have those studies underway.

“We delivered a lead small-molecule compound to reprogram the cell’s software to force it to re-express VEGF-A,” Disney says. “Transforming [it] into a potential medicine that reaches patients will take considerably more time and research.”

The very discovery of a large number of small-molecule materials that bind RNA with a very high affinity and selectivity creates opportunities for pharmaceutical companies to embark on medicinal computations to find more drug-like binders. Scripps published their findings ahead of time.

“We analyzed the entire pathway for how the protein is silenced, and then we used that information to identify how to reinvigorate its expression.”

The current dataset of RNA binders by 20-fold. The chemical potential simulation predicts the chemical potential of drug targets, taking the field of natural product drug discovery to the realm of de novo, drug target-driven, natural product drug discovery for the first time, Pfošt points out. “It’s a first for the field, and one which expands Lodo’s reach to new targets that might not have previously been accessible.

“The next step is modeling in conjunction with bioinformatic gene cluster molecular predictions and SAR, as well as in the context of combinatorial SynBio. This is an exciting area with great promise for Lodo’s new platform of drug discovery.”

Lodo acquired all of the assets of Conifer Point Pharmaceuticals, and is housing Conifer Point’s technology at its New York City-based facilities. John Kulp Jr., Ph.D., chief technology officer at Conifer Point and inventor of its technology, has joined Lodo as vice president, Cheminformatics. Conifer Point founder and CEO, John Kulp III, Ph.D., is serving as a retained consultant to Lodo, Pfošt mentions, “Several other Conifer Point personnel have joined Lodo as employees or are working with us as retained consultants.”

Pfošt noted that Lodo has planned for other targeted strategic acquisitions, and sure enough, the company announced on Sept. 3 that it had also completed the acquisition of Hibiskus BioPharma, Inc. Financial details of the transactions were not disclosed.

In a related transaction, Lodo acquired exclusive worldwide rights from the University of California, Riverside and Michigan State University to preclinical proteasome and immunoproteasome inhibitors developed by the co-founders of Hibiskus. Lodo says that these two transactions will enable the company to consolidate the proteasome inhibitor portfolio and related intellectual property, know-how and early-stage research.

The lead preclinical molecule, TIR-199—now known as LODO-141—is an irreversible and potent hybrid cyclic peptide proteasome inhibitor from the syrbaatin natural product family. LODO-141 is structurally distinct from marketed proteasome inhibitors, retains activity against chemo-resistance to these inhibitors and is highly selective, with a well-characterized mechanism of action.

“Today marks the completion of our first acquisition strategy,” says Pfošt. “The magic is when this modeling capability is brought to bear on natural product drugs that are either known from historical databases or imputed from modeling of biosynthetic gene clusters.”

The potential of this new platform is clear to Lodo’s senior team in executing value-creating transactions. We believe these novel protease inhibitors are an excellent fit for Lodo,” Pfošt commented in a press release. “Early studies conducted at the NCI and elsewhere suggest that LODO-141 may have utility in treating solid tumors. We intend to assess its potential as a single agent and also in combination with cancer immunotherapy.”
“Partnering with biotech companies that have innovative approaches to drug discovery is an essential part of Roche’s research strategy,” says James Sabry, head of Roche Pharma Partnering. “We are excited about Jnana’s small-molecule approach to targeting SLC transporters, which represent a promising class of targets for discovering new medicines for patients across a range of diseases.”

The collaboration grew from a longstanding connection between Roche’s global head of immunology discovery, Kara Lassen, and Jnana’s founders. Lassen had previously worked at the Broad Institute in Cambridge, Mass., in the group of Jnana co-founder Rammik Xavier, and she was familiar with SLC biology and kept up with the science,” Kotz points out. “The connection catalyzed the deal talks that happened between Jnana and Roche at this year’s J.P. Morgan meeting in January. The deal came together really quickly from that point, and Roche moved with astonishing speed.”

SLC transporters are an important class of more than 450 human membrane proteins that are gatekeepers for controlling the movement of metabolites in and out of cells and organs. This protein family is diverse in structure and mechanism, with a wide range of substrates and cellular localities. SLCs ensure metabolites are present in the right place at the right time, which is crucial for health and often dysregulated in disease.

“SLC transporters are strongly linked to human diseases biology but under-explored, with only 20 of the 450 SLC transporters currently targeted by approved drugs. At Jnana, we believed a systematic approach was required to open up this target class,” continues Kotz.

“We select our therapy areas based on diseases where metabolites—the chemical building blocks and nutrients essential for life—play a central role, and where there is an SLC transporter that can be targeted to modulate the metabolite level,” she says. “We have built our internal, propriety RAPID platform and leveraged this platform to advance programs targeting SLC transporters in immune-mediated, neurological and metabolite-dependent diseases.”

The drug discovery and research activities under the Roche-Jnana collaboration will leverage Jnana’s RAPID platform, which is designed to overcome the challenges of directly targeting SLC transporters. The RAPID platform is a cell-based, proprietary platform that can be used to screen small-molecule libraries to identify novel modulators of any SLC transporter.

“We look forward to a highly collaborative relationship with Roche, in which Roche’s disease area expertise and leading R&D capabilities complement Jnana’s pioneering work in SLC biology and drug discovery. This agreement with Roche highlights the value of our RAPID platform, which is breaking new ground for targeting SLC transporters with a systematic, highly efficient approach—with the goal of realizing the potential of this rich target class to discover new medicines for patients,” stated Dr. Joel Barrish, co-founder and chief scientific officer of Jnana.

“Roche and Jnana both have a shared confidence in SLC transporters as targets in immune and neurological diseases, and Roche recognized that Jnana’s RAPID platform provides an effective drug discovery approach to this target class,” Kotz adds. “Jnana is also very excited to be advancing our own internal pipeline of programs modulating SLC transporters for other diseases, in addition to our programs with drug partners.”

DISCOVERY

Understanding lupus one cell at a time

JAX team finds distinctive interferon gene expression signature across wide variety of blood cells

BY MARK WANNER OF JAX

BAR HARBOR, Maine—Systemic lupus erythematosus (SLE), the most common type of lupus, is an autoimmune disease that affects a variety of tissues, including joints, skin, brain and kidneys. It is difficult to diagnose, has unknown causes, and is often dysregulated in disease.

JAX team finds distinctive interferon gene expression signature across wide variety of blood cells. While interferon expression is important in controlling virus infections, it is dysregulated in many autoimmune diseases, including SLE. Understanding the role of interferon in SLE is critical because interferon deregulation can drive inflammation and tissue injury.

A large team led by Jackson Laboratory (JAX) professor Dr. Jacques Banchereau and Dr. Virginia Pascual—director of the Drukker Institute for Children’s Health at Weill Cornell Medicine—has genomically profiled 276,000 peripheral blood mononuclear cells from 44 children (33 with SLE, 11 matched healthy controls) and 82,000 cells from 14 adults (eight with SLE, six matched healthy controls).

“This was a huge effort across several institutions,” says Banchereau. “It was also the first study to comprehensively compare SLE samples from both children and adults.”

The results revealed a distinctive interferon signature with altered gene expression in subpopulations of cells across a wide variety of blood cell types. While interferon deregulation has long been associated with SLE, the single-cell genomic profiling in this study mapped increased expression of interferon-stimulated genes to unique blood cell populations. Importantly, it confirmed that the gene expression signatures are similar in both children and adults with SLE. The study also showed that the interferon signature is more prominent in more severe cases.

Also, while most lupus cases do not follow a Mendelian pattern of inheritance, rare cases are caused by genetic mutations in any one of about a dozen genes. Interestingly, the study found expression of that group of genes in small subsets of dendritic cells, which function to sensitize the immune system to outside antigens and protect against autoimmunity.

“That was a surprise,” says Banchereau. “Data reveal a more important connection than previously thought between dendritic cells and SLE pathogenesis.”

The paper provides a roadmap for SLE researchers for further target discovery, adding to the prospects for better SLE diagnostics, patient stratification in clinical trials and eventually more targeted therapies.

“We have been investigating this story for more than 20 years,” says Banchereau. “And now, especially within the last two years, we’re seeing significant progress being made for the benefit of SLE patients.”
Editor’s Focus: Nearing year’s end and looking forward

BY JEFFREY BOULEY

B ECAUSE WE SHIFTED TO A 10-ISSUE schedule around the middle of this year, this October issue is the next-to-last one for the year 2020. But before we get to the “end” of this year in the next issue, I wanted to let you know that we have some exciting new improvements for you both before and after Jan. 1.

We’ve been teasing on our covers our new logo and some of our upcoming offerings, as well as rolling out several improvements already, from our revamped e-newsletters to our new e-book offerings (with a neuroscience e-book already available and an immuno-onychology one coming soon) to webinars and podcasts. Later this year, we plan to unveil a totally refurbished website that will be available for both desktop and mobile, and as a virtual platform.

And as anyone who has worked in science knows, this is not the sausage into which you look until you understand the bigger picture.

Jeffrey Bouley, DDN Chief Editor

OUT OF ORDER: SAUSAGE-MAKING

BY RANDALL C WILLIS

I ADMIT THAT I AM ADDICTED TO A delicacy found throughout downtown Toronto: the sausages grilled daily on hot dog carts.

Affectionately known as street meat or smog dogs, these amazing comestibles tantalize the taste buds with a heavenly combinatin of fat and spices. Whenever someone visits Toronto, I insist that they take me for a smog dog run as we sample the varied cuisine across the city.

That said, there is one simple rule on which I insist: Never look directly into the sausage. Nothing good will come of anyone knowing what they are ingesting. Revel, I say, in the sensory pleasures of ignorance.

Although this intro could be easily linked to the Special Report on Metabolic Disorders found elsewhere in this issue, it instead connects to the challenges of practicing science and medicine in front of a live audience as organizations of all stripes struggle to develop vaccine penetration of vaccine misinformation campaigns. It feels like we are losing ground with those communities that once accepted immunization.

As reported elsewhere, a small group of U.S. citizens were asked in March if they would be willing to take a COVID-19 vaccine, and 80 percent reported they would. As May came to an end, that number had dropped to 67 percent. Also in May, a poll of U.S. citizens suggested that only 42 percent would be willing to take the vaccine, whereas 27 percent confirmed they wouldn’t. The remainder were unsure.

If this were just down to the anti-vaccine move alone, it would have been easier to explain. But it is not. The situation only gets worse. Witness the 35 percent of the population to achieve eradication, international, African and local agencies somehow managed to achieve that incredible goal through campaigns as much community relations as clinical.

Closer to home, we all watch as organizations work to become the first to launch a vaccine, or more likely, several vaccines, for COVID-19 onto the market. Already, countries like Canada, the United States and the United Kingdom have placed orders for millions of doses of vaccine that haven’t yet completed testing.

And yet, at the same time that clinical organizations and health departments discuss who should receive the first doses off the line, the general public is starting to express a louder and louder ambivalence at the potential of immunization.

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How can the identification of new or alternative transcripts enhance drug discovery? Noncoding RNAs (ncRNA) and alternatively spliced transcripts of disease-associated genes are gaining momentum as potential drug targets (reviewed in Matsui and Corey 2017 and Zhao et al., respectively). Although only about two to three percent of the human genome codes for protein-coding mRNAs (collectively called the exome), many other RNAs—including ncRNA—also impact gene expression in healthy and diseased tissues, making them potential targets for drug discovery. Indeed, there are ongoing clinical studies for compounds that target ncRNAs or pre-mRNAs implicated in several diseases, including Duchenne muscular dystrophy (DMD), spinal muscular atrophy (SMA), hematological malignancies and solid tumors; see Matsui and Corey 2017.

When an mRNA molecule is transcribed from its respective gene as a pre-mRNA, it contains exons—the segments that code for protein domains or for regulatory regions in the mature mRNA—and introns, which are removed during splicing. As reviewed in Zhao et al., this has become increasingly apparent that many—perhaps even most—genes in the human genome yield multiple, alternatively spliced mRNAs containing various combinations of exons, and that these alternative transcripts lead to proteins with diverse functional domains.

Thus, alternative splicing has significant implications for drug development, identification of biomarkers, and our understanding of drug resistance—especially as many drug targets target specific protein domains. Examples of diseases caused by mis-spliced mRNAs include neurodegenerative disorders, cancer and tumor progression, immune diseases, cardiovascular disease, and metabolic disease; examples of mis-spliced genes include SRSF1, BCL2L1, Cyclin D1, KLF6 and VEGF. As described in Zhao et al., RNA-seq has enabled the identification of drugs that are specifically targeted to disease-causing splice variants in SMA, DMD and other diseases.

What are the different types of RNA-seq workflows, and when is each most appropriate? There are several types of RNA-seq workflows (described briefly below), but each begins with the isolation of RNA from the sample, followed by construction of an RNA-seq library for sequencing on an NGS instrument. If you are primarily interested in the expression of protein-coding genes under a specific set of conditions, then a workflow that enriches for mRNA is appropriate. These methods work best with high-quality RNA and depend on the fact that most eukaryotic mRNA molecules have a polyA tail that can be used to selectively enrich for mRNA using beads coated with stretches of complimentary thymine bases (oligo dT). The final sequencing data is then enriched for protein-coding transcripts.

If you are seeking a more comprehensive view of the transcriptome, including non-coding RNA and pre-mRNA, then select a whole-transcriptome sequencing (WTS) workflow; this is a good choice for degraded RNA samples also. For WTS, the workflow typically includes a polyA depletion step, which removes the highly abundant ribosomal RNA (rRNA), which provides no useful information for most gene expression studies. In addition to the methods above, there are also many workflows for scRNA-seq, as well as options for custom-enriched libraries to enable more focused sequencing of specific transcripts. Such targeted workflows enable efficient use of sequencing. Conversely, it is also possible to selectively deplete highly expressed transcripts that may make it difficult to detect the expression of lowly expressed genes; one example is the targeted depletion of globin transcripts from blood-derived samples.

Out of all of the existing methods for examining the transcriptome, RNA-seq offers the most comprehensive method for studying differential gene expression and changing levels of noncoding RNAs at both the single-cell and bulk sequencing levels. RNA-seq thus offers a powerful tool of investigative tools for understanding the molecular basis of disease and for the discovery and testing of new treatment options. **


Commentary: RNA-seq in preclinical research and drug discovery—digging deep for insights

BY DR. RACHEL WEST OF ROCHE
BRIEFS

**MiMedx aims to boost R&D with new hire**

MARIBETTA, Ia.—August saw MiMedx Group Inc. expand its management team with the addition of Dr. Robert B. Stein as the company’s new executive vice president of research and development. Stein has more than 40 years of experience in drug discovery and development, having previously served at firms such as Merck, Ligand Pharmaceuticals, DuPont-Merck and Incyte Pharmaceuticals, among others.

“Throughout my career I’ve been drawn to research efforts and companies that are taking on meaningful and challenging health problems,” said Stein. “MiMedx is taking the next steps to further the science and better understand the clinical potential of placental tissue to bring improved healing to more people in need. My role is to continually enhance the rigor of our strong scientific foundation that will more clearly inform our pipeline and expand the company’s potential to address significant areas of unmet clinical need.”

**COVID-19 resources meant to streamline pandemic efforts**

WALTHAM, Mass.—PerkinElmer Inc. recently launched two free-access Perkin Elmer COVID-19 Data Dashboards—the PerkinElmer COVID-19 Drug Compound Dashboard and the PerkinElmer COVID-19 Clinical Trial Dashboard—as online resources for the scientific community as efforts continue to find antivirals and vaccines for the virus. The dashboards are supported by the company’s Signals Lead Discovery and the TIBCO Spotfire advanced analytics platform, which offers a robust option for searching and aggregating drug candidate and clinical trial data. The first dashboard enables users to search through 1.6 million drug compounds and interrogate the CAS COVID-19 Antiviral Candidate Compound Dataset, a curated chemical substance dataset provided by CAS, a division of the American Chemical Society. The second dashboard pulls trial data from sources such as clinicaltrials.gov on trial status, compounds of study and other relevant information.

**Better health with humanin?**

BY LORI LESKO

LOS ANGELES—A new study led by researchers at the University of Southern California (USC) Leonard Davis School of Gerontology has demonstrated that humanin, a peptide encoded in the small genome of mitochondria, has a huge impact on longevity and healthier lives in both animals and humans. Perhaps the most compelling finding is that humanin could be a key factor to lowering risk for diseases such as Alzheimer’s disease (AD).

Dementia, of which Alzheimer’s is the most common form, affects an estimated 36 million people worldwide, according to the National Institutes of Health (NIH). This number is expected to rise to 115 million by 2050 unless an effective therapeutic is developed.

“Humanin has long been known to help prevent many age-related diseases, and this is the first time that it has been shown that it can also increase lifespan,” says senior author Dr. Pinchas Cohen, a professor of gerontology, medicine and biological sciences and dean of the Leonard Davis School of Gerontology.

“While there have been many studies examining the effects of humanin in preventing AD in animal models, it was our observation that humanin declines with age in several species—combined with the fact that humanin treatment can prevent many age-related diseases—that gave us the idea that humanin would be involved in the general aging process,” Cohen tells DDN.

“The biggest takeaway would be that humanin can both increase healthspan and lifespan of model organisms, and this study suggests that it could be a novel anti-aging peptide for humans,” he adds. “The anti-AD properties of humanin have been known for a while, and this recent study combined with our previous studies extends the known beneficial effects of humanin to lifespan and healthspan extension.”

Kelvin Yen, a research assistant professor at USC Leonard Davis School of Gerontology and first author of the paper, comments, “This study has been a culmination of nearly 10 years of work to uncover structural details of proteins and protein-complexes, even in highly complex samples. Despite its power, the technique has however suffered from limited analytical depth due to the low reaction efficiency of the used reagents,” according to the paper. “With the introduction of enrichable cross-linking reagents like PhoX, this can partly be resolved.”

“With these reagents the sample complexity can be reduced, focusing only on peptides modified by the cross-linking reagent, forming mono-linked and cross-linked peptide products. Further improvements are however still required to fully unlock the potential of XL-MS, as the mono-linked peptides do not provide the sought-after structural information and typically make up more than half of the sample load after enrichment,” the study states.

“We described the development of a novel acquisition approach utilizing ion mobility to physically separate the mono-linked from the cross-linked peptides, providing better signal-to-noise to the latter class of ions,” the authors note. “Additionally, we present a novel acquisition technique to uncover structural details of proteins and protein-complexes, even in highly complex samples. Despite its power, the technique has however suffered from limited analytical depth due to the low reaction efficiency of the used reagents,” the paper says. “With the introduction of enrichable cross-linking reagents like PhoX, this can partly be resolved.”

**Utrecht and Bruker team up on mass spec methods**

BY MEL J. YEATES

BILLERICA, Mass.—In August, Bruker Corp. announced a collaboration with Utrecht University to advance the study of the 3D structures and interactions of proteins by mass spectrometry.

The Heck Lab at Utrecht University has been a leader in proteomics and the study of protein structure and interactions by mass spectrometry for over two decades. Dr. Richard Schelter has recently joined the Heck Lab as group leader to focus on crosslinking mass spectrometry (XL-MS) for structural and interaction proteomics.

The collaborative work will focus on the development of trapped ion mobility spectrometry (TIMS) and parallel accumulation of fragments (PASEF) methods, along with crosslinkers and XL-MS software for the timsTOF Pro 4D-Protomics mass spectrometer.

“We are delighted to work with Bruker on the further development of workflows for XL-MS that take advantage of the speed of PASEF and the unique large-scale, accurate CCS [collision cross sections] data to enhance the detection of crosslinks in XL-MS,” said Dr. Albert Heck of Utrecht University. “We are excited by the initial results published in Molecular and Cellular Proteomics and look forward to advancing XL-MS even further. We are also interested in other applications of ion mobility separation and CCS on the timsTOF Pro to glyco-proteomics and top-down proteomics.”

The CCS workflows have been described in a paper entitled “Benefits of Collision Cross Section Assisted Precursor Selection (caps-PASEF) for Cross-linking Mass Spectrometry.”

“Having personally been involved in some of the conceptual work in XL-MS in 2001 at Sandia National Laboratory, I believe the advances made by Heck’s group will make this technique more routinely available for structural biology studies using the timsTOF Pro,” noted Dr. Gary Kruppa, vice president of proteomics at Bruker. “Our collaboration with Utrecht University will accelerate adoption of XL-MS within the broader structural and interaction proteomics community.”

“XL-MS represents a powerful approach to uncover structural details of proteins and protein-complexes, even in highly complex samples. Despite its power, the technique has however suffered from limited analytical depth due to the low reaction efficiency of the used reagents,” the paper says. “With the introduction of enrichable cross-linking reagents like PhoX, this can partly be resolved.”

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HUMANIN

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A decade worth of data that we have been slowly accumulating. The in vivo studies are more recent having been performed in the past few years. The next steps are to determine how humanin achieves all these beneficial effects... to humans.

Humanin has been found in the animal kingdom throughout evolution, according to the study, which was published online in the journal Aging. Researchers examined humanin in worms, mice and humans including Alzheimer’s patients and the children of centenarians.

“The results highlight the potential for humanin and other mitochondrial proteins to become treatments for age-related ailments and indicate that humanin may be an ancient mitochondrial signaling mechanism that is key for regulating the body’s health and lifespan,” states Yen.

At the same time, he notes that humanin levels have previously been observed to decrease with age in many species. In this new study, the scientists observed higher levels of humanin in organisms pre-disposed to long lives, including the age-resistant naked mole rat, which experiences only a very slow decline in levels of humanin circulating in the body throughout its 30-year lifespan.

“In contrast, mice experience a 40-percent drop in humanin over the first 18 months of life, and primates such as rhesus macaques appeared to have a similarly dramatic drop in humanin between the ages of 19 and 25,” Yen points out.

In humans, researchers observed higher and more sustained levels of humanin in 18 children of centenarians versus a control group of 19 children of non-centenarians, according to Yen. Individuals whose parents reach 100 years old are statistically more likely than other people to reach a very old age.

The study reports that in some newborn cord blood samples, high levels of humanin correlated with a high mitochondrial DNA copy number, or the number of copies of the mitochondrial genome present within each cell.

“Humanin levels are inversely correlated with a decrease in mitochondrial DNA copy number, which in itself has been associated with a number of different diseases such as cancer, kidney disease and cardiovascular disease,” says Yen.

“This study, as well as many others, suggests that humanin administration would be an effective therapeutic treatment for a large number of diseases, and further solidifies the importance of the mitochondria beyond its traditional role as the ‘powerhouse of the cell,’” Cohen concludes.

While the bulk of the work was performed by Cohen and Yen at USC, this research was a multi-university effort by more than 20 authors at eight universities and was supported by multiple funding sources.

“The biggest takeaway would be that humanin can both increase healthspan and lifespan of model organisms, and this study suggests that it could be a novel anti-aging peptide for humans.”

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WHERE SCIENCE INTERSECTS INNOVATION

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GOING AFTER GLIOBLASTOMA

Purdue team looks to harness natural killer cells to fight cancer

BY KELSEY KAUSTINEN

WEST LAFAYETTE, Ind.—While no cancer is what anyone would consider “easy” to treat, brain cancers are at the top of the list for difficulty, given limited treatment and surgical options. In fact, glioblastomas, the most common malignant brain tumor type, generally come with an estimated survival time of only 12 to 18 months from diagnosis. The issue is not just the location, but also the nature of glioblastoma—in addition to being extremely immunosuppressive, glioblastoma is resistant to treatment and very heterogeneous, with no single guaranteed mutation to target. The cancer takes advantage of multiple immunosuppressive mechanisms to evade the immune system.

How? A research team from Purdue University is looking to turn the immune system back onto these tumors by genetically modifying natural killer (NK) cells, a type of immune cell, to specifically target cancer cells.

“Multifunctionally engineering these cells is a potentially transformative way to enable the improved treatment of this disease,” Sandro Matosevic, an assistant professor in Purdue’s College of Pharmacy, commented. “Our solution is the first multifunctional, responsive immunotherapy harnessing natural killer cells to specifically target cancer cells. By targeting multiple mechanisms at the same time, we severely limit the ability of GBM to avoid treatment.”

The Purdue team is working with the Purdue Research Foundation Office of Technology Commercialization to license its patent-pending technology, as well as seeking partners to further develop this approach.

The Matosevic lab published an article this summer in the Journal of Hematology & Oncology that discussed some of the team’s efforts to leverage NK cells as a cancer treatment. Their work—which appeared in a paper titled “CD155 immunoregulation as a target for natural killer cell immunotherapy in glioblastoma,” authored by Matosevic and Kyle B. Lupo—focused on the CD155 antigen in particular.

“CD155 or poliovirus receptor (PVR), has recently emerged as a pro-tumorigenic antigen, overexpressed on GBM and contributing to increased GBM migration and aggressiveness,” the authors explained. “CD155 has also been established as an immunomodulatory receptor, able to both activate NK cells through interactions with CD226 (DNAM-1) and CD96 and inhibit them through interaction with TIGIT. However, NK cell TIGIT expression has been shown to be upregulated in cancer, establishing CD155 as a predominately inhibitory receptor within the context of GBM and other solid tumors, and rendering it of interest as a potential target for antigen-specific NK cell-based immunotherapy.”

“CD155 modulates the immunoregulation of T and NK cells through interactions with TIGIT, DNAM-1, and CD96—with, in particular, interactions between TIGIT and CD155 thought to result in severe immunosuppression of NK and cytotoxic T cells in the tumor microenvironment (TME),” Lupo and Matosevic continued, noting that the antigen’s overexpression plays a role in cell proliferation and cancer cell migration.

“By targeting this axis in NK cells, through engineered cell therapies and combinatorial antibody/cell therapy approaches, it is possible to suppress CD155-induced inhibition and enhance the natural cytolytic functions of NK cells,” Lupo and Matosevic point out that while TIGIT/CD155-induced immunosuppression isn’t the target, several other preclinical studies by other organizations are underway to assess the efficacy of engineered NK cells in glioblastoma. A trial being conducted at the Johann Wolfgang Goethe University Hospital is exploring “CAR-NK-92 cells engineered with a second-generation CAR targeting HER2,” they report, and other teams are looking at targets such as EGFRvIII, CXCR4, EGFR and Erb2.

“Not only is cell-based immunotherapy a highly unique and promising treatment approach, but natural killer cells have been shown to be able to kill GBM with high efficiency. They are also considered safer than other cell-based therapies such as T cells. In addition, it has been shown that clinically, patients benefit from a higher presence of NK cells in the tumor microenvironment,” Matosevic remarked.

XL-MS

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engineered natural killer cells. By targeting multifunctional, responsive immunotherapy in a press release. “Our solution is the first improved treatment of this disease, ” Sandro Matosevic, an assistant professor in Purdue’s College of Pharmacy, commented. “This focuses the acquisition, a feature largely beneficial for complex mixtures.”

The Matosevic lab published an article that discussed some of the team’s acquisition, a feature largely beneficial for complex mixtures.

TO enhance the study of 3D structures and interactions of proteins, Bruker Corp. and Utrecht University are working together on merging crosslinking mass spectrometry with trapped ion mobility spectrometry and parallel accumulation serial fragmentation methods.

Advanced analysis software is key, as XL-MS data is more complex and even more information-rich than typical shotgun proteomics experiments. Scheltema is working on enabling the innovative XlinkX software to process TIMS/PASEF data, and making it available to the community of timsTOF Pro users.

“My group intends to push the boundaries of PASEF to enhance XL-MS workflows by making them CCS-aware,” added Scheltema. “We have a significant ongoing effort in bioinformatics applied to analyzing XL-MS data using our XlinkX software. We are excited to work with the open data format architecture of the timsTOF Pro in XlinkX to develop code that can use large-scale, accurate CCS values for the identification of crosslinks and to further improve false discovery rate calculations.”
**PRECLINICAL**

**BRIEFS**

**A new approach to toxicity testing**

WINSTON-SALEM, N.C.—As part of the Innovation Quarter’s iQ Healthtech Labs, the Wake Forest Institute for Regenerative Medicine (WFIRM) and Oracle Health Sciences have joined forces to establish a consortium of industry, government and academia members to investigate new approaches to confirming the safety of drug candidates before they enter human trials. The collaboration will apply WFIRM’s Body-on-a-Chip technology to assess drug toxicity in a variety of human tissues, and the resulting data will be analyzed with machine learning technology being co-developed by Oracle Labs and Oracle for Research. “Being able to create approaches to medicine that take into account an individual’s unique genetic makeup is critical in today’s world of medicine,” said Jane Shen, head of sector development for the Innovation Quarter. “That’s why iQ Healthtech Labs is focused on creating partnerships like this one with WFIRM and Oracle that bring together powerful leaders to advance innovative solutions.”

**One step closer**

EDINBURGH, Scotland—Ingenza Ltd. reported on its expertise in sustainable and cost-effective influenza vaccine technology. “We are proud to be applying our company’s expertise in increasing memory immune response to a stable cell line that permanently lacked PTB. After a few weeks, there were very few fibroblasts left, and the whole dish was filled with neurons. Thus, the team discovered that inhibiting or deleting just a single gene—the gene that encodes PTB—transforms several types of mouse cells directly into neurons. More recently, Fu and Dr. Hao Qian, another postdoctoral researcher in his lab, took the finding a big step forward, applying it in what could one day be a new therapeutic approach for Parkinson’s disease and other neurodegenerative diseases. Just a single

**Down-regulating PTB**

One-time Parkinson’s treatment generates new neurons

BY ILENE SCHNEIDER

SAN DIEGO—Dr. Xiang-Dong Fu has long studied the basic biology of RNA and the proteins that bind it. A single discovery has launched Fu into neuroscience. Fu and his team at University of California, San Diego (UCSD) School of Medicine have been studying a protein called PTB that is well known for binding RNA and influencing which genes are turned “on” or “off” in a cell. To do this, they used siRNA to manipulate cells to reduce the amount of that protein. A postdoctoral researcher then convinced Fu to use a different technique to make a stable cell line that permanently lacked PTB. After a few weeks, there were very few fibroblasts left, and the whole dish was filled with neurons. Thus, the team discovered that inhibiting or deleting just a single gene—the gene that encodes PTB—transforms several types of mouse cells directly into neurons. More recently, Fu and Dr. Hao Qian, another postdoctoral researcher in his lab, took the finding a big step forward, applying it in what could one day be a new therapeutic approach for Parkinson’s disease and other neurodegenerative diseases. Just a single

**Second-gen COVID vaccine in development**

OSE Immunotherapeutics leverages cancer vaccine to develop CoVepiT

BY KRISTEN SMITH

NANTES, France—Building on demonstrated success with a vaccine targeting non-small cell lung cancer, French biotech OSE Immunotherapeutics has developed a promising pharmaceutical approach to combat SARS-CoV-2. Their candidate, called CoVepiT, leverages the company’s expertise in increasing memory immune response activated by leukocytes, rather than harnessing an antibody response. According to their paper “Tissue-resident memory CD8 T-cell responses elicited by single injection of a multi-target COVID-19 vaccine,” which was recently published on BioRxiv, the vaccine technology uses artificial intelligence algorithms to increase T memory cell responses.

**MSCs demonstrate efficacy in preclinical lung disease study**

Cynata Therapeutics cites positive data in rodent model of IPF

BY DDN STAFF

MELBOURNE—Cynata Therapeutics Ltd., a clinical-stage biotechnology company specializing in cell therapeutics, recently announced positive efficacy data from a study of its induced pluripotent stem cell (iPSC)-derived Cymerus mesenchymal stem cells (MSCs) in a preclinical rodent model of idiopathic pulmonary fibrosis (IPF). IPF is a currently incurable disease of unknown cause, which results in extensive scarring or fibrosis of the lungs. Lung damage is often advanced by the time the condition is initially diagnosed, and existing treatment options have very limited efficacy. It invariably progresses to respiratory failure, with only 20 to 30 percent of patients surviving five years from the time of diagnosis. The value of the global IPF market is expected to reach around $5.9 billion by 2025, with an annual growth of 13 percent.

These latest results with Cymerus MSCs add to the large body of evidence on the potency of these cells and their potential utility in treating a wide range of devastating diseases,” said Dr. Kilian Kelly, chief operating officer of Cynata. “IPF

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treatment to inhibit PTB in mice converted native astrocytes, star-shaped support cells of the brain, into neurons that produce the neurotransmitter dopamine. As a result, the mice's Parkinson's disease symptoms disappeared. The study was published June 24, 2020, in Nature.

"Researchers around the world have tried many ways to generate neurons in the lab, using stem cells and other means, so we can study them better, as well as to use them to replace lost neurons in neurodegenerative diseases," said Fu, a distinguished professor in the department of cellular and molecular medicine at UCSD's medical school.

"The fact that we could produce so many neurons in such a relatively easy way came as a big surprise."

Several methods can be used to mimic Parkinson's disease in mice. The UCSD researchers applied a dopamine look-alike molecule to poison neurons that produce dopamine. As a result, the mice lose dopamine-producing neurons and develop symptoms similar to Parkinson's disease, such as movement deficiencies. The researchers developed a noninfectious virus that carries an antisense oligonucleotide sequence—an artificial piece of DNA designed to specifically bind the RNA coding for PTB, thus degrading it, preventing it from being translated into a functional protein and stimulating neuron development.

Antisense oligonucleotides, also known as designer DNA drugs, are a proven approach for neurodegenerative and neuromuscular diseases pioneered by study co-author Dr. Don Cleveland. It now forms the basis for a U.S. Food and Drug Administration (FDA)-approved therapy for spinal muscular atrophy and several other therapies currently in clinical trials. Cleveland is chair of the Department of Cellular and Molecular Medicine at UC San Diego School of Medicine and member of the Ludwig Institute for Cancer Research.

"The mechanism is to down-regulate the RNA binding protein PTB, which removes its competition for a specific miRNA (miR-124) to attack the REST complex," Fu explained. "The REST complex is responsible for suppressing the microRNA as well as a large number of neuronal specific genes. PTB itself is a target of miR-124. Therefore, once PTB is initially down-regulated, miR-124 will be more efficient in down-regulating REST, which leads to the induction of miR-124 to further down-regulate REST. During this process, PTB is also further down-regulated by miR-124. This loop keeps going until PTB is totally gone and REST largely suppressed, thus a large number of neuronal specific genes turned on to generate new neurons."

"Parkinson is characterized by lost dopaminergic neurons in the brain," he continued. "Dopaminergic neurons originate in a midbrain region called substantia nigra and project their axons to striatum to release dopamine. This circuitry is damaged in Parkinson's disease patients, which is accompanied with emulsification of surrounding non-neuronal cells called astrocytes. By down-regulating PTB in astrocytes in substantia nigra are converted to dopaminergic neurons to connect to striatum, thereby restoring dopamine to reverse the disease phenotype."

The next steps include the demonstration of the strategy in large animal models, evaluating the safety issues and further refining the procedure. If all goes well, it will be ready for clinical trials, according to Fu, who adds that, "Because there is no cure for Parkinson's and many other neurodegenerative diseases, our strategy provides a new and efficient way to generate new neurons in specific brain regions to replace lost ones in specific disease setting and address a wide range of neurological diseases."

"It's my dream to see this through to clinical trials, to test this approach as a treatment for Parkinson's disease, but also many other diseases where neurons are lost, such as Alzheimer's and Huntington's diseases and stroke. What if we could target PTB to correct defects in other parts of the brain, to treat things like inherited brain defects? I intend to spend the rest of my career answering these questions," he concluded.
MSC CONTINUED FROM PAGE 13

represents an enormous unmet medical need, as existing treatment options have only modest effects on disease progression and survival rates.”

It is notable that fibrosis is observed in the lungs of COVID-19 patients with severe disease and may become an important factor in the longer-term effects in such surviving patients, the company notes. It also occurs in surviving patients of acute respiratory distress syndrome from other causes. As previously announced, Cynata is conducting a Phase 2 clinical trial in patients with respiratory distress associated with COVID-19.

The effect of Cymerus MSCs is being studied in the widely used and clinically relevant bleomycin-induced IPF model, which is the gold-standard preclinical model of this condition, according to Cynata. Compared to placebo, the Cymerus MSC treatment led to statistically significant improvements in:
- Dynamic lung compliance (the lung’s ability to stretch and expand)
- Airway resistance (a measure of the airway’s opposition to airflow into the lungs)
- Interstitial lung inflammation (swelling in the tissue surrounding the airways)
- Interstitial lung fibrosis (fibrosis in the tissue surrounding the airways)
- Epithelial and subepithelial thickness (additional signs of fibrosis).

The initial phase of the IPF preclinical study found that control animals suffered a 40 percent loss of dynamic lung compliance after bleomycin administration, as expected in this model. However, when Cymerus MSC treatment was administered in a single dose three weeks later, or as a double dose at three and four weeks later, the loss of dynamic lung compliance was just 15 percent. Similarly, while bleomycin administration led to profound interstitial inflammation and fibrosis, as well as increases in airway resistance, epithelial thickness and subepithelial thickness, Cymerus MSC treatment dramatically reduced each of these harmful effects.

The study is led by Prof. Chirshan Samuel of the Department of Pharmacology at Monash University, following on from his previous studies which demonstrated that Cymerus MSCs significantly reduce fibrosis and inflammation in a model of asthma.

Commented Samuel: “These results are extremely encouraging. While they are very consistent with our previous studies of these cells in a model of asthma, it was important to confirm that the potent anti-inflammatory and anti-fibrotic effects of Cymerus MSCs would be replicated in IPF, which is a disease with very different underlying pathophysiology. We look forward to publishing our results in a peer-reviewed journal in due course.”

OSE CONTINUED FROM PAGE 13

immunity in the oncology space. The methodology employs “sentinel” cells present in barrier tissues such as the respiratory tract and the lungs. This barrier tissue effectively serves as the interface between the external world and the body. When the sentinels, or memory leukocytes, encounter danger at the barrier, they migrate into the cell to initiate the immune response. What makes the OSE approach function is the activation of those cells that “remember” the peptides of the virus as it approaches, which can then eliminate infected cells before significant virus replication. Because of the nature of its attack on the body, this same technology can be applied to fight SARS-CoV-2.

“The CoVepiT program is based on a clinically validated technology now shown to induce tissue-resident memory T lymphocytes (Trm) sentinel response against multiple parts of SARS-CoV-2, suggesting it provides a long-term protective immunity, as opposed to transient protection provided by neutralizing antibodies,” explained Nicolas Poirier, chief scientific officer of OSE. “In addition, this vaccine is designed to anticipate ongoing recurrent virus mutation and evolution, further adding to its long-term protective potential.”

In seeking to take the successful oncology approach into the realm of COVID-19, OSE studied the immune systems of patients who had recovered from the virus—those with moderate, severe or asymptomatic presentations of COVID-19, as well as MERS, a previous coronavirus. They were able to identify the path of the virus as well as a small peptide of the virus that was recognized by the lymphocytes of the convalescing survivors.

After mapping this hallmark of the immune system of cured patients, the team analyzed 46,000 different sequences of the virus from all over the world. In preparing their trial vaccine, they were careful to screen out the mutations found in small, regional hotspots to drive a broadly effective response. However, the methodology does allow for further mutation and evolve, a feature of many cancerous processes. Scientists have watched the coronavirus evolve for 15 years, and logically believe that it will continue to do so while conserving existing peptides as well, making CoVepiT nimble enough to attack future iterations.

“We’ve shown that we can quickly modify the technology [from cancers] to COVID. Tomorrow, we can change a peptide using the same technology and drawing on what was learned from healed COVID and MERS patients,” asserts Poirier.

The first generation of COVID-19 vaccine trials may have lacked effectiveness because of the virus’s ability to escape the weapon and mutate, a feature of many cancerous processes. In the advanced trials for the non-small cell lung cancer vaccine, the researchers are aiming at five different targets within the tumor. In the COVID trials, they are targeting 11, so if the virus mutates in one target, there remain 10 more potential successes. This multi-target approach promises high potential on its own, or in conjunction with the many antibody approaches currently in development.

“We are building a second-generation vaccine built for the long term, using learning from the first generation. We do not target antibody response, we target a 2-lymphocyte vaccine response,” Poirier concludes. “Our approach may also complement an antibody approach—perhaps with a first vaccine for antibodies and a second 2-lymphocyte vaccine for longer-term immunity.”

OSE Immunotherapeutics has developed what it thinks is a promising prophylactic approach to combat SARS-CoV-2, based on previous success with a vaccine targeting lung cancer.

“We are rapidly advancing our fight against COVID-19, a major public health issue, with a vaccine program especially designed for people at risk, including older adults and immunocompromised population.”

Alexis Peyroles, CEO of OSE Immunotherapeutics
INTERCEPTING DIABETES

Researchers target autoimmunity, not hyperglycemia

BY RANDALL C WILLIS

At the tender age of 11, Elizabeth Hughes Gossett was given a death sentence; she was diagnosed with diabetes. It was 1918.

At the same time, in Canada, Frederick Banting was working on the isolation of a hormone called insulin, first from the pancreases of dogs and later from fetal calves. Between late 1920 and 1921, alongside Charles Best, J.J.R. Macleod and James Collip, Banting was able to reproducibly isolate insulin. In early 1922, he set up a clinical practice that ultimately saved Gossett’s life.

A century later, insulin still holds center court in the treatment of diabetes and management of hyperglycemia, particularly for patients with type 1 diabetes (T1D). Technical innovations have occurred since those early days, but treatment remains lifelong. Over her remaining 58 years of life, Gossett received approximately 42,000 insulin injections.

Beyond glycemic control

“But the question is: Alright, we can control T1D, but how well can we really control it?” Leon asks. “When you look at HbA1c levels, they are elevated in 70 percent of subjects despite insulin. So clearly, in the real world, insulin is not offering full satisfactory resolution of the problem.”

He also notes that insulin doesn’t prevent many of the complications—cardiovascular and metabolic, mostly—associated with T1D, complications that shorten lifespans. Also, patients can expect to have lifespans of 10 to 16 years less than if they didn’t have diabetes, he adds, noting that this, too, “is despite insulin, so there is an unmet need.”

Prevention was founded on the question: Can we act earlier in the disease process?

“I talk to patients about this so many times because they always ask us, why haven’t you cured this disease yet or why haven’t you prevented this disease yet?” recounts Chantal Mathieu, head of Clinical Endocrinology at KU Leuven and coordinator of INNODIA, a T1D public-private partnership. “I always say it’s not because of lack of trying.”

She offers several reasons why T1D proves particularly challenging.

Firstly, it affects such a small tissue: the insulin-producing beta cells, which are well hidden within the islets of Langerhans, which are buried within the pancreas, which is buried deep in the abdomen by more predominant organs.

“If you are studying arthritis, you just have to look at the joints to see if they’re inflamed,” Mathieu explains. “You can stick a needle in them and you can get tissue. Beta cells are less than 1 percent of the whole tissue of the pancreas, and it’s very well hidden away, so we cannot access them.”

Furthermore, by the time clinicians begin to see changes in blood glucose levels, more than 70 percent of the beta cells are dysfunctional or destroyed.

“We need better ways of imaging what is happening with the beta cell,” Mathieu presses. “And we need faster ways of testing interventions that can point the way to what we want to do.”

This was partly the impetus behind INNODIA, which has undertaken integrated biomarker research using peptidomics, proteomics, immunomics and many other omics.

According to Leon, there are 40 to 50 genetic markers for predisposition to autoimmunity and T1D. But even with these markers, disease onset doesn’t typically occur without a second trigger, such as changes in immune regulation or viral infection (more on that later).

“When the immune system tries to eliminate the Coxsackievirus B, which goes into the beta cells that make insulin, the collateral damage is the destruction of the beta cells,” he explains. “And because there is loss of tolerance against the beta cell antigens, there’s also destruction of unaffected beta cells.”

It is this destruction that launches the tetrad of key biomarkers: autoantibodies against insulin, insulinoma-associated protein 2 (IA-2), zinc transporter 8 (ZnT8)
and glutamic acid decarboxylase (GAD65).

“Once you have two of the four autoantibodies, you have the disease,” Leon continues. “There’s no way back. There is no restoration of tolerance, and people will progress towards destruction of beta cells and eventually clinical TID.”

So, how do you treat somebody who doesn’t know they need treatment?

“We believe we are entering a new era in medicine here, when people may be able to be treated before the disease starts,” says Leon, “like [the film] Minority Report, just for medicine.”

It will require screening asymptomatic people at high risk of developing disease, which he suggests is already happening in some European countries—Finland, for example, already screens half their population for TID autoantibodies—but may see significantly slower uptake in North America.

Even if we do manage to diagnose TID before it becomes problematric, however, how do we interrupt or reverse the pathology?

Find and replace

Recent efforts to reverse the damage caused by beta cell loss by companies such as Sernova, Sigilon and Viacyte have attempt

ed to leverage both stem cell and cell encapsulation technology to replace the missing cells.

“The strategy here is as long as you can eliminate cell-cell contacts—between the host tissues and your graft cells—you will protect against the adaptive immune destruction, allograft rejection or autoimmunity,” explained ViaCyte’s chief scientific officer, Kevin D’Amour, in the September 2019 DDN Special Report on Stem Cells. “So, the materials we use are blocking cells, but they’re wide open from a molecular perspective, so even large molecules and antibodies can flow through.”

The effort continues to be challenged by finding the right balance of proteins, seeking those involved in mechanisms of beta cell regeneration, including transdifferentiation, neogenesis from ductal precursor cells and beta cell replication.

In STZ-induced mouse models, the researchers found that liraglutide improved blood glucose levels and increased beta cell mass, although this effect was lost after treatment withdrawal. They also noted the presence of bi-hormonal islet cells, a transcription factor specifically expressed in beta cells, highlighting alpha-to-beta cell transdifferentiation.

“Our findings indicate that, in autoimmune diabetes, alpha cells are facing an intense regenerative state in an effort to maintain human beta cells that are not producing insulin and sulphite and sulphite into inactivated T cells. “It is reasonable to speculate that the continuous presence of liraglutide is required for the maintenance of islet beta cell mass by promoting the main mechanism responsible for the improvement of blood glucose levels in treated mice, at least during the first 30 days of treatment stages,” the authors concluded.

Using a systems biology approach to drug repositioning, the researchers curated a library of proteins, seeking those involved in mechanisms of beta cell regeneration, including transdifferentiation, neogenesis from ductal precursors and beta cell replication.

Moving to autoimmunity

But whether you’re looking at transplantation or new DKO mouse models, the researchers found that liraglutide improved blood glucose levels and increased beta cell mass, although this effect was lost after treatment withdrawal. They also noted the presence of bi-hormonal islet cells, a transcription factor specifically expressed in beta cells, highlighting alpha-to-beta cell transdifferentiation.

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“Once you have two of the four autoantibodies, you have the disease,” Leon continues. “There’s no way back. There is no restoration of tolerance, and people will progress towards destruction of beta cells and eventually clinical TID.”

So, how do you treat somebody who doesn’t know they need treatment?

“We believe we are entering a new era in medicine here, when people may be able to be treated before the disease starts,” says Leon, “like [the film] Minority Report, just for medicine.”

It will require screening asymptomatic people at high risk of developing disease, which he suggests is already happening in some European countries—Finland, for example, already screens half their population for TID autoantibodies—but may see significantly slower uptake in North America.

Even if we do manage to diagnose TID before it becomes problematric, however, how do we interrupt or reverse the pathology?

Find and replace

Recent efforts to reverse the damage caused by beta cell loss by companies such as Sernova, Sigilon and Viacyte have attempt

ed to leverage both stem cell and cell encapsulation technology to replace the missing cells.

“The strategy here is as long as you can eliminate cell-cell contacts—between the host tissues and your graft cells—you will protect against the adaptive immune destruction, allograft rejection or autoimmunity,” explained ViaCyte’s chief scientific officer, Kevin D’Amour, in the September 2019 DDN Special Report on Stem Cells. “So, the materials we use are blocking cells, but they’re wide open from a molecular perspective, so even large molecules and antibodies can flow through.”

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Moving to autoimmunity

But whether you’re looking at transplantation of ex vivo-produced beta cells or transdifferentiation of alpha cells to beta, the challenge of autoimmunity is ever present.

“I think that’s the problem also with organoids,” says Astrid Doern, study director at Crown Biosciences. “I would imagine that even if you transplanted them into the pancreas, and if you even get proper engraftment and vascularization, if it’s still the same individual, you run into the same problem as organ transplantation.”

“You would have to suppress the whole immune system,” she adds. “Otherwise you’ll get similar reaction again.”

Thus, rather than focus on the beta cells, other organizations like ProventionBio are focusing on the immune response and the challenge of autoimmunity.

In the 1980s, says Mathieu, clinicians observed cyclosporine to patients newly diagnosed with TID to modulate autoimmunity. Others have tried bone marrow transplantation to arrest beta cell destruction.

“And more recently,” she adds, “short-term interventions with compounds like anti-thymocyte globulin or anti-CD3 antibodies like teplizumab have given clinicians the ability to freeze destruction for months or years.”

Teplizumab is at the heart of the disease intervention component of Provention’s approach to TID.

“We believe anti-CD3 is a very logical choice for T cell-driven autoimmunity because CD3 is the main activator of T cells,” Leon explains. “And it was found that you could treat T cell diseases by either depleting the T cell or by providing a deactivation signal to the T cells.”

Numerous earlier efforts to apply anti-CD3 immunotherapies to TID met with frustration, however, as early promise gave way to inimenable toxicity issues.

According to Leon, many of those early molecules and the ones still being developed in cancer are immune depletion agents, which trigger cytokine release as they kill immune cells and increase the risks of infection. Teplizumab has a different mechanism of action.

Engineered by Jeffrey Bluestone at the University of Chicago and later at the University of California, San Francisco, teplizumab is designed to provide the deactivation signal. converting autoreactive T cells into inactivated T cells.

“He modified the antibody not to bind to Fc receptors, which are the responsive party for cytokine release and cell depletion,” explains

Changing channels: By modifying the autoantigen with a thioductose motif, immunopentane bound to antigen-presenting cells can induce maturation of naive CD4 T cells toward a cytolytic phenotype. 

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

“I talk to patients about this so many times because they always ask us, why haven’t you cured this disease yet or why haven’t you prevented this disease yet? I always say it’s not because of lack of trying,” says Chantal Mathieu, coordinator of INNODIA.
**DIABETES**

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Leon. “So he achieved for the first time an anti-CD3 that was well tolerated and achieved its target results in clinical studies.”

Across three Phase 2 trials, teplizumab demonstrated significant protection of beta cells in newly diagnosed T1D. Macrogenics licensed the antibody and initiated the Phase 3 PROTEGE study with Eli Lilly. Unfortunately, as Leon presses, the FDA required the primary endpoint of the study to include the change in HbA1c rather than C-peptide, which had been used in Phase 2 studies.

“If you do a trial right, you shouldn’t see a difference in HbA1c between active and placebo because physicians treat to a target of HbA1c by giving more or less insulin,” he continues. “So, what you should see is the same HbA1c with less insulin use, and that’s what was seen with teplizumab in clinical studies.”

PROTEGE missed its primary endpoint, which Leon says was devastating for the field as results supported a positive impact on beta cell protection, based on C-peptide, causing Lilly to step away.

Provention picked up the license and is in the process of repeating the Phase 3 study in newly diagnosed patients (PROTECT) after making improvements in the trial design and going back to C-peptide as the primary endpoint.

Macrogenics had also licensed teplizumab to TrialNet to conduct the TN-10 prevention trial. The study was performed on non-diabetic relatives of people living with T1D, who had at least two diabetes-related autoantibodies and showed evidence of dysglycemia in an oral glucose tolerance test. And although the ages of the subjects ranged from eight to 50 years, 72 percent were younger than 18 years.

When the study ended, the median time to T1D diagnosis was 48.4 months in the teplizumab group versus 24.4 months in the placebo group. Similarly, roughly twice as many subjects on teplizumab were diabetes-free (57 vs. 28 percent).

In June, at the ADA conference, the researchers announced that another year had been added to the median time to diagnosis. They also suggested that not only did teplizumab slow the decline of C-peptide levels, but in some cases, the decline reversed, indicating possible recovery of dysfunctional beta cells.

“We moved straight into filing a rolling Biologics License Application,” Leon says. “We plan to complete the submission in the fourth quarter of this year for the delay or prevention of clinical T1D in subjects with Stage 2 T1D, who are at risk of progressing.”

Imcyse is taking a different approach with its Imotope platform, using the mechanism of autoimmune targeting against itself by modifying the autoantigen with a thioeductase motif.

In this case, when antigen-presenting cells (APCs) deliver a modified autoantigen to naive CD4 T cells, the thioeductase motif directs T cell maturation toward a cytolytic phenotype. These cells then destroy, in an antigen-specific manner, all APCs presenting the same autoantigen, as well as other effector T cells interacting with the same APCs.

In 2016, Jean-Marie Saint-Remy and colleagues at Imcyse and University of Leuven described the impact of this approach in mice, using the GAD65 autoantigen.

They reported that not only was the diabetes-free survival rate significantly increased in immunized mice (82 percent vs. 38 percent untreated), but also GAD65-induced cells were able to induce apoptosis in APCs presenting the peptide.

Perhaps just as importantly, the researchers also saw signs of the bystander effect in immunized mice as the GAD65-induced cells triggered the destruction of other autoantigen-presenting APCs.

“The present technology using a single epitope of a single beta cell antigen potentially prevents responses toward alternative epitopes and perhaps even alternative antigens, provided the latter are presented by the same APC,” Saint-Remy and colleagues wrote. “This condition is easily achieved considering that the main site at which the CD4+ T cells control the immune response is in the lymph nodes draining the diseased organ, a location at which much of the autoantigens released into the affected organ are processed for presentation to the immune system.”

Last September, Jean Van Ramplebergh, vice president of clinical and regulatory at Imcyse, presented the results of a Phase 1b trial of the insulin-based Imotope IMCY-0098 at the EASD congress in Barcelona. These data suggested that IMCY-0098 was safe in patients.

The company is currently preparing for its follow-on clinical trial IMPACT, which Van Ramplebergh says will have an adaptive design, allowing the company to adjust study parameters as new results come in or milestones are achieved.

A key focus for this study will be the search for biomarkers, which was not as successful as expected in earlier studies, in part because of the status of the appropriate technologies at the time.

“Now, we can benefit from other and more precise, more specific techniques to really go and look at what is the immune response after a certain number of injections, after a certain dosing, and based on that, decide what to move forward and how to test then more adults and adolescents,” Van Ramplebergh continues.

An additional motivation for the biomarker analysis is Imcyse’s participation in INNODIA, which, he presumes, has led the company to collect many more samples that they would never collect if left to their own devices.

“This will allow [INNODIA members] to build a biobank through all the different studies and add on this collection to be able to follow all these all the markers,” he explains. “That’s something that you would probably not do or not so extensively on your own, because

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**Same target, different mechanism:** Unlike other anti-CD3 antibodies that are immune depletion agents, triggering cytokine release as they kill immune cells and increase the risks of infection, PreventionBio’s teplizumab was designed to provide a deactivation signal, converting autoreactive T cells into inactivated T cells.

**Bystander effects:** After interacting with Imotopes, the newly cytolytic T cells not only destroy antigen-presenting cells (APCs) delivering autoantigen, but also other effector T cells interacting with the same APCs.

“If you are studying arthritis, you just have to look at the joints to see if they’re inflamed. You can stick a needle in them and you can get tissue. Beta cells are less than 1 percent of the whole tissue of the pancreas, and it’s very well hidden away, so we cannot access them.”

Chantal Mathieu, coordinator of INNODIA

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**CREDIT:** IMCYSE
you would probably not elaborate on so many aspects.”

Also looking to turn the immune system against itself, City of Hope’s Bart Roep and colleagues at Leiden University Medical Center recently reported on their efforts to transform tolerogenic dendritic cells with proinsulin peptide.

“We want to negotiate with the immune system rather than bombard it into submission, because the latter may affect your chances of fighting off cancer and infections, including coronaviruses,” Roep explained in an announcement. “In addition, this is the first time that physicians tried to intervene in T1D years after diagnosis.”

In a small Phase 1 study in patients with long-standing T1D, the researchers found that both beta cell function and overall diabetic control remained stable throughout the six months of monitoring.

“Most importantly, there were no signs of systemic immune suppression, no induction of allergy to insulin, no interference with insulin therapy, and no accelerated loss in beta cell function in patients with the remaining C-peptide,” the authors reported. “Our results warrant subsequent clinical testing in patients with a shorter diagnosis of T1D and with preserved C-peptide production, to assess whether this novel intervention strategy is able to delay or halt progressive loss of beta cell function.”

Taking the vaccine concept one step further, Provention is targeting one of the other factors believed to be involved in the onset of T1D pathology— infection with Coxsackievirus B. The infectious disease work started in Finland, explains Leon, which struggled with elevated rates of autoimmune disease compared to neighbouring Russia.

“Finland created a national program called DIPP—Diabetes Prediction and Prevention—which followed 220,000 consecutive newborns,” Leon recounts. “They collected samples from the mothers and from the babies every three months, and followed those with genetic predisposition to T1D until they were at least 15 years of age.”

The researchers then examined the samples from those who developed clinical T1D and found that 60 percent of those children had experienced a persistent infection with Coxsackievirus B within the six to 12 months preceding onset of clinical T1D.

The later TEDDY study of 400,000 children performed a complete virome analysis to look for infections associated with T1D, and Coxsackievirus B came to the top.

“A consortium called nPOD—Network for Pancreatic Organ Donors—collected pancreas from patients who donated their organs to science, and found 60 percent of those subjects had Coxsackie B inside their beta cells,” Leon continues.

Other work showed that the virus uses a cell receptor expressed in insulin granules, closing the loop on why Coxsackievirus B infects beta cells.

A vaccine against Coxsackievirus B being developed by Vactech caught the eye of Provention co-founders Leon and CEO Ashleigh Palmer, who were then focused on celiac disease through their previous company Celimmune. They licensed the vaccine as Provention’s first asset.

In May, Karolinska Institutet’s Malin Flosstrom-Tullberg and colleagues described their evaluation of Provention’s polyvalent Coxsackievirus B vaccine candidate in non-human primate and mouse models.

Not only did the vaccine protect the animals from infection, but also completely protected permissive mice from developing virus-induced diabetes. Unlike in the unvaccinated controls, the islets of immunized mice showed strong staining for insulin and glucagon.

“Our results provide a solid scientific basis for human trials with Provention’s PRV-101 vaccine,” said study co-author Tampere University’s Heikki Hyöty, who is also a co-founder of Vactech, in announcing the findings. “Our observation showing that this prototype works in macaques is highly important since their immune system closely resembles the immune system of humans.”

According to Leon, Provention is in the process of initiating a first-in-human clinical trial, which will start by the end of the year in Finland.

“This is potentially the first ever vaccine for Coxsackie B and is also potentially the first ever vaccine designed for autoimmunity,” he says. “In addition to preventing the acute infection by Coxsackievirus B—which can cause myocarditis, pericarditis, meningoitis—the virus has these potential complications of celiac and T1D, which we want to prevent.”

Viruses are unlikely to be the only microbes influencing the autoimmune process and subsequent glycemic control.

Microbial mixers
“Microbiome in diabetes research has been the focus for our group for many, many years,” says Jim Wang, senior vice president at CrownBio. “People realize that gut microbiome impacts the glucose regulation and also impacts the pancreas function.”

And as Bernat Olle, CEO of Vedanta Biosciences, suggested in the DDN Special Report on Microbiomics in January 2019, the microbiome also significantly influences the immune system.

“It turns out that about 80 percent of the immune cells in the body are in the gut,” said Olle. “They have to patrol all of the populations of microbes that are sending signals to the body and make sure that they’re behaving themselves properly.”

Accessing and profiling the gut microbiome in the experimental setting continues to be a challenge, Wang adds, and this is vital to understand the impact of therapy or diet in these models.

“One conventional method is to use the endoscope to insert into the gut to take some samples to measure and profile those microbiomes,” he says. “But that’s invasive and difficult and expensive. It’s not quite feasible to do that in humans and in the animal models.”

Thus, CrownBio and its CVMD group have been collaborating with a company to develop a simple capsule-like device that a patient or test
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animal—right now, nothing smaller than a monkey—can swallow. Thus, the issue raised by Doerner is experimental and model consistency.

“We moved facilities in San Diego and that was a huge challenge for our team,” she recounts. “We had to make sure that we had a working IBRD [irritable bowel disease] model and other models. So, we basically tried to transfer the microbiome.”

Part of that effort, she describes, involved moving old bedding to the new facilities, simply to maintain consistency.

“Unfortunately, the vendor is not always having a consistent microbiome either,” she adds. “So, we’ve had issues [where we] literally had to try some different vendors to get a reliable model.”

Doerner gives the example of their collagen-induced arthritis model, where changes in the microbiome can translate to 30 percent of mice getting disease or 80 to 90 percent of mice.

“We had to do a lot of tweaking to make sure that it keeps consistent, so we can actually offer that to our clients,” she says. “If it only works in 30 percent of the mice, that’s not a good starting point for [clients].”

Another significant challenge comes in making sure you are studying the microbiome that matters most to drug development: the human gut microbiome.

According to Doerner, companies have expressed interest in establishing human microbiomes in mice for their IBRD models, but, she adds, that is not an easy task.

“First of all, you have to have mice that don’t have a microbiome or get rid of the microbiome they have,” she says. “And then, how stable is the microbiome from a human in a mouse over time? So, I think there are a lot of challenges.”

Those challenges aside, microbiota profiling has started to show subtle differences between the microbiomes of subjects with islet autoimmunity and T1D and those without.

As was recently reviewed by Emrah Altindis and colleagues at Boston College and Linköping University, two studies performing metagenomics sequencing of stool samples from the TEDDY study identified several bacteria that weakly correlated with T1D onset.

Similarly, the DIABIMMUNE study of approximately 1,000 children followed from one month to three years of age observed diminished microbial diversity and reduced bacterial gene content in autoantibody-positive children as they progressed toward T1D.

“A functional analysis found that bacterial metabolisms in autoantibody-positive subjects is characterized by a higher prevalence of genes involved in sugar transport and a lower prevalence of genes associated with amino acid biosynthesis compared to subjects that did not convert,” recounted Altindis and colleagues.

The authors are quick to note, however, that despite the growing catalogue of microbes identified as more prevalent in T1D, any causal relationship is poorly understood. And in fact, the identity of the microbiome may be less important than its function in the gut ecosystem.

Looking to turn a possible hazard into a weapon, KU Leuven’s Conny Gossett.

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Francisco Leon, chief scientific officer of ProventionBio

“People who need people”

**GIVEN THE CURRENT TREATMENT OPTIONS, ORIGINALLY TYPE 1 DIABETES REPRESENTS A LIFE LONGLASTING OF GLYCEMIC CONTROL EFFORTS AND CONSTANT CONCERNS ABOUT SECONDARY, POSSIBLY LIFE-THREATENING COMPLICATIONS. FOR THIS REASON, A KEY FEATURE OF CHANTAL MATIEU’S INVOLVEMENT AS COORDINATOR AT INNODIA IS THE ROLE OF THE PATIENT ADVISORY COMMITTEE IN HELPING THE ORGANIZATION TO DECIDE WHERE ITS T1D RESEARCH SHOULD GO.”

She recounts, “This is not feasible. This is too much blood. This is too frequent.”

Too often, she says, when patients ask clinicians what something means, the clinicians misinterpret the request as the desire for clarification, for the same information using different words. Instead, patients are asking why something is being done. What value the therapy brings. What will be different at the end of the day.

“I have learned so much from them, because they look at this very critically,” she acknowledges. “So, I really like having these people living with the disease involved in our projects.”

“We have colleagues who have T1D in their families,” he explains. “And they remind us every day what it is to live with T1D and the practical realities of the disease and celiac as well. So, we really try to consider and take into account patient preferences and needs as much as possible in our trials.”

“Even when I was at Sanofi, I’ve always been a big fan of involving patients and patient committees. I have experienced just over the last two, three months how helpful [the committee] was and how proactive they are when we reach [out] to them.”

Jean Van Ramplebergh of Imcyse

And being responsive can come in the smallest gestures.

The dosing schedule for teplizumab was originally 14 days, says Leon, but families found that burdensome as it meant losing two weekends.

“We found a way, doing PK/PD modeling, to compress the 14 into 12 days so that it’s only one weekend, but giving exactly the same amount of drug by increasing the dose a little bit,” he explains.

“And we found that this method, which we are using in PROTECT, gives patients better quality of life by not having to worry about the second weekend.”

Imcyse’s vice president of clinical and regulatory, Jean Van Ramplebergh, shares their enthusiasm.

“Even when I was at Sanofi, I’ve always been a big fan of involving patients and patient committees,” he says. “I have experienced just over the last two, three months how helpful [the committee] was and how proactive they are when we reach [out] to them.”

When it comes to recognizing that all of this work—mechanism of action, dosing strategy, formulation, etc.—is meaningless in the absence of the unique perspectives of those living with T1D, the researchers speak with one voice: the patient’s.
BRIEFS

Ascendis files BLA for growth hormone deficiency drug

COPENHAGEN, Denmark—Ascendis Pharma A/S is a biopharmaceutical company that uses its novel TransCon technologies to address unmet medical needs, recently announced that the FDA had accepted the company’s Biologics License Application (BLA) for TransCon hGH (lonapegsomatropin), an investigational long-acting prodrug of somatropin (human growth hormone or HGH) for the treatment of pediatric growth hormone deficiency (GHD).

Based on data from its clinical development program, we believe once-weekly TransCon hGH has the potential to expand treatment options for clinicians and children with GHD,” said Dr. Dana Pizzuti, Ascendis Pharma’s senior vice president of development operations.

TransCon HGH is designed to release somatropin with the same mode of action and distribution as once-daily somatropin products. The BLA for pediatric GHD is supported by the results of a clinical development program that included eight clinical trials evaluating safety and efficacy in more than 400 subjects with GHD.

FDA gives green light for ENSASARC trial

SAN DIEGO—The FDA has cleared the pivotal ENSASARC trial protocol, TRACON Pharmaceuticals announced in August. The company plans to begin enrolling participants in the trial, which will evaluate evafolimab, in the fourth quarter of this year. ENSASARC will be a multi-center, open-label, randomized study of sarcoma patients with one or two prior cancer therapies and no prior immune checkpoint inhibitor therapies. The trial has an enrollment goal of 160, with patients randomized evenly into two cohorts: one that will evaluate evafolimab as a single agent, and one that will evaluate the combination of evafolimab and Yervoy. Objective response rate will be the primary endpoint.

“Immune therapy has radically changed the treatment paradigm for a number of cancers, and we hope evafolimab will do the same for sarcoma patients who have few treatment options,” said Dr. James Freddo, chief medical officer of TRACON.

One and done for HIV?

AGT begins Phase 1 clinical trial on potential gene therapy cure for HIV/AIDS

ROCKVILLE, Md.—Taking a giant step toward a potential “one-and-done” cure for HIV/AIDS, American Gene Technologies (AGT) reports the U.S. Food and Drug Administration (FDA) recently cleared the path for a Phase 1, first-in-human clinical trial for AGT’s lead HIV program, AGT103-T. In September, researchers began enrolling people for the trial from the Baltimore/Washington, D.C. area, hotspots for HIV/AIDS, with data expected by the end of 2020.

The purpose of the trial is to investigate the safety of AGT103-T, measure key biomarkers and explore surrogate markers of efficacy. AGT103-T is a single-dose, lentiviral vector-based gene therapy developed to eliminate HIV from the patient. This genetically modified cell product is made from a person’s own cells, and focuses on repairing key immune system damage done by HIV and allowing the patient’s natural responses to control the virus. AGT’s approach is designed to repair the T helper cell defect and provide durable virus control that is not compromised by HIV strains.
AGT103-T

CONTINUED FROM PAGE 21

It has been nearly 40 years since the first cases of HIV/AIDS in the United States were discovered. Today, 38 million people globally—including 1.2 million in the United States—are infected with the disease.

“...is a third-generation prodrug and new chemical entity that modulates glutamate, the most abundant excitatory neurotransmitter in the human body. The primary mode of action of troriluzole is normalization of synaptic levels of glutamate. Troriluzole increases glutamate uptake from the perisynaptic space by augmenting the expression and function of excitatory amino acid transporters located on glial cells that play a key role in clearing glutamate from the synapse.

According to Coric, “We advanced troriluzole in a series of proof-of-concept trials to assess signal detection across disease states. Our strategy is to only further invest in troriluzole indications where we find an emerging drug signal. We are pleased to report these OCD study results that show a consistent and clinically meaningful drug effect at all study timepoints in patients who had an inadequate response to existing standard-of-care treatments. This study provides our R&D team with the necessary data to refine and adequately power subsequent trials to advance troriluzole in OCD.”

Phase 3 study of two doses of troriluzole versus placebo.

“Most treatments for OCD target the brain neurotransmitter serotonin, but a large number of patients treated with SSRIs do not fully respond to treatment,” he added. “Multiple lines of evidence suggest that the brain neurotransmitter glutamate plays an important role in OCD symptoms. Troriluzole normalizes brain glutamate levels, and it is hypothesized that normalizing glutamate levels may be therapeutic in OCD.”

Coric explained that he ran the Yale OCD Research Clinic prior to his career in drug development, and his academic research at Yale focused on the use of glutamate modulating drugs in OCD and other neuropsychiatric disorders.

“Glutamate is the most abundant excitatory neurotransmitter in the brain; when levels are high, it could cause or worsen a number of neuropsychiatric disorders,” he noted.

Dr. Christopher Pitterner—who is associate professor of psychiatry, director of the Yale OCD Research Clinic and an investigator in the trial—commented, “OCD affects one person in 40 and can be debilitating. Fully a third of patients do not respond to current treatments, and many who do respond continue to suffer from residual symptoms. New therapies are urgently needed to alleviate this suffering and disability. There has not been a mechanistically novel medication approved for OCD in over 20 years. If troriluzole proves to be effective for these patients, it would be a huge advance. I look forward to working with Biohaven to explore the data from this proof-of-concept trial in more depth to inform the design of future pivotal studies.”

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Phase 3 study of two doses of troriluzole versus placebo.

“Most treatments for OCD target the brain neurotransmitter serotonin, but a large number of patients treated with SSRIs do not fully respond to treatment,” he added. “Multiple lines of evidence suggest that the brain neurotransmitter glutamate plays an important role in OCD symptoms. Troriluzole normalizes brain glutamate levels, and it is hypothesized that normalizing glutamate levels may be therapeutic in OCD.”

Coric explained that he ran the Yale OCD Research Clinic prior to his career in drug development, and his academic research at Yale focused on the use of glutamate modulating drugs in OCD and other neuropsychiatric disorders.

“Glutamate is the most abundant excitatory neurotransmitter in the brain; when levels are high, it could cause or worsen a number of neuropsychiatric disorders,” he noted.

Dr. Christopher Pitterner—who is associate professor of psychiatry, director of the Yale OCD Research Clinic and an investigator in the trial—commented, “OCD affects one person in 40 and can be debilitating. Fully a third of patients do not respond to current treatments, and many who do respond continue to suffer from residual symptoms. New therapies are urgently needed to alleviate this suffering and disability. There has not been a mechanistically novel medication approved for OCD in over 20 years. If troriluzole proves to be effective for these patients, it would be a huge advance. I look forward to working with Biohaven to explore the data from this proof-of-concept trial in more depth to inform the design of future pivotal studies.”
OPTIMAL trial points to new option for acromegaly treatment

BY KELSEY KAUSTINEN

NEEDHAM, Mass.—A key issue in both clinical trials and regular disease management is patient compliance, particularly when it comes to treatments and therapeutics that are delivered via injection. Biopharmaceutical company Chiasma Inc. is one company working to address that stumbling block by offering more oral options, specifically with its Mycapssa (octreotide) capsules. Chiasma reported in August that data from its Phase 3 CHIASMA OPTIMAL clinical trial were published in the Journal of Clinical Endocrinology & Metabolism in a paper titled “Maintenance of acromegaly control in patients switching from injectable somatostatin receptor ligands to oral octreotide therapy.”

OPTIMAL was aimed at assessing the safety and efficacy of Mycapssa capsules in acromegaly patients who previously demonstrated biochemical control while receiving injectable somatostatin analogs (SSA), specifically octreotide LAR or lanreotide. Fifty-six patients with biochemically controlled disease were enrolled and randomized to receive either Mycapssa or placebo, titrating up from 40 mg per day to 80 mg per day. The trial met its primary and all secondary endpoints.

Within the Mycapssa cohort, 77.7 percent of patients maintained growth hormone levels, compared to 30.4 percent in those on placebo. Seventy-five percent of Mycapssa patients successfully completed the trial without requiring reversion to their prior injectable treatment, and those that did revert re-established baseline response levels after just one dose. Mycapssa was well tolerated, with no new or unexpected safety signals observed.

Mycapssa received FDA approval as a long-term maintenance treatment for acromegaly patients in June, specifically for those patients who have responded to and can tolerate treatment with octreotide or lanreotide. The approval marks Mycapssa as the first and only oral somatostatin analog approved by the FDA.

“This publication in a top-tier respected journal provides validation in the scientific community of our pivotal study results and the potential benefits Mycapssa could bring to patients with acromegaly [with] a novel, non-injectable oral option,” said Dr. William Ludlam, senior vice president of clinical development and medical affairs at Chiasma.

Acromegaly is a condition in which a benign pituitary tumor produces too much growth hormone, resulting in side effects such as intense headaches, joint pain and impaired vision. If it progresses, it can result in health conditions such as type 2 diabetes, hypertension, respiratory disorders, and cardiac and cerebrovascular disease. While the preferred treatment is surgery to remove the tumor, not all patients are eligible for surgery and must rely on somatostatin receptor ligands (SRLs) instead. Injectable SRLs require deep-tissue injection, and “can be associated with substantial treatment burden or deleterious long-term sequelae, including injection site pain, nodules, bruising, inflammation, and scarring,” according to the paper. In addition, while some patients can receive their injections at home, the authors report that only 17 percent of patients do so, and “With the majority of SRL injections occurring in the health care delivery setting, patients report a burden to their everyday life, including impacts from travel and administration time in addition to lost work.” According to Chiasma, roughly 8,000 patients with acromegaly are chronically treated with somatostatin analog injections in the U.S.

Patient compliance in the OPTIMAL trial was extremely high, “with a mean compliance of 98.2 percent in the OOC group and 96.9 percent in the placebo group,” the authors reported.

“Reflecting the positive experience of patients and their clinicians with OOC [oral octreotide capsule] treatments in this trial, 90% of patients receiving OOCs at the end of the DPC [double-blind placebo-controlled] period chose to remain on active treatment in an OLE [open-label extension] phase . . . This pivotal placebo-controlled study indicates that OOCs may be an effective option in patients with acromegaly currently responding to injectable SRLs, while potentially avoiding side effects and compliance issues related to injectable regimens,” they concluded.

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BRIEFS

Diagnostic monitoring for methotrexate

WALTHAM, Mass.—Echosens has highlighted new guidelines jointly issued by the American Academy of Dermatology and the National Psoriasis Foundation regarding the safety and efficacy of commonly prescribed medications for psoriasis, including methotrexate. The immunosuppressive drug has been linked to a variety of side effects on the liver, and Echosens notes that such guidelines provide support for increased use of non-invasive assessment tools such as its VCTE (FibroScan), an elastography technology.

Jon Gintchik, CEO of Echosens North America, said, "The AAD/NPF guidelines add to the growing evidence that direct assessments of liver health with FibroScan—a rapid, reliable and non-invasive tool—can serve as an essential part of overall health management. We are gratified by the growing recognition that liver health assessment with FibroScan can play an important role in the effective and safe management of many chronic conditions, as evidenced by these guidelines for patients with psoriasis undergoing long-term methotrexate use."

AmoDx, HaiHe aim for CDx

XIAMEN, China—AmoDx Diagnostics Co. Ltd. (AmoDx) and HaiHe Pharmaceutical have inked an agreement for the development of a companion diagnostic test to support HaiHe’s novel MET inhibitor glumetinib. Per the agreement, AmoDx will develop and register the AmoDx Pan Lung Cancer PCR Panel (9-in-1 Plus) in Japan in order to get PMDA approval for an intended use as a c-MET exon14 skipping companion diagnostic for glumetinib in non-small cell lung cancer.

"We announce with great excitement this co-development collaboration for the Japan market," stated Dr. Li-Mou Zheng, founder and CEO of AmoDx. "AmoDx has a strong pipeline of diagnostic products for precision medicines, as well as successful CDx development experience of AmoDx. "AmoDx has a strong pipeline of diagnostic products for precision medicines, as well as successful CDx development experience with FibroScan—a rapid, reliable and non-invasive tool—can serve as an essential part of overall health management. We are gratified by the growing recognition that liver health assessment with FibroScan can play an important role in the effective and safe management of many chronic conditions, as evidenced by these guidelines for patients with psoriasis undergoing long-term methotrexate use."

Todos announces positive data for new point-of-care saliva-based test

BY KRISTEN SMITH

REHOVOT, Israel—Pharmaceutical companies across the globe are scrambling to create resources to help stem the proliferation of COVID-19 and modulate its lethality. The first step in effective prevention and mitigation is accurate, timely, widespread testing, which remains a key target for companies and their potential customers.

Todos Medical, an Israeli in-vitro diagnostics company, has announced positive proof-of-concept data for a 10-minute, rapid point-of-care saliva-based test for detecting active SARS-CoV-2 infections. Todos has built its business on engineering diagnostics for early detection of a

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ADVANCING A SARS-CoV-2 ANTIGEN TEST

Avacta and LSTM collaborate to clinically validate saliva-based rapid coronavirus test

BY MEL J. YEATES

CAMBRIDGE & WETHERBY, U.K.—Avacta Group plc recently announced a collaboration with the Liverpool School of Tropical Medicine (LSTM) to clinically validate the rapid, saliva-based point-of-care (POC) coronavirus antigen test Avacta is developing with Cytiva.

"(This) is an important partnership which provides Avacta with access to patient samples both in the U.K. and abroad, where the incidence of the disease is currently much higher, to ensure prompt access to a sufficient number of samples for clinical validation," stated Dr. Alastair Smith, CEO of Avacta. "We have been working with the Liverpool School of Tropical Medicine for some time to define the target performance specifications of the saliva-based rapid test and their insight has been tremendously helpful in this regard."

LSTM was founded in 1898 as the first institution in the world dedicated to research and teaching in tropical medicine. LSTM has a research portfolio of around £320 million, with projects and partnerships in over 70 countries.

"The partnership between Avacta and LSTM exemplifies the role of the LSTM in translational work to advance products to market, and we are pleased to be working with Avacta on this coronavirus antigen test," added Dr. Lisa Baldwin, business development manager, LSTM.

Under the terms of the collaboration, LSTM will carry out the clinical validation of the Avacta COVID-19 antigen rapid saliva test in their category 3 laboratories on patient samples. In addition to working with the UK government’s CONDOR program—which provides Avacta with access to patient samples in the United Kingdom—the partnership with LSTM provides the opportunity to access patient samples in Africa and South America. The higher prevalence of the disease in these regions means that samples for prospective clinical validation studies are more readily available.

"LSTM has access to real patient samples in Africa and South America where disease prevalence is much greater," says Dr. Alastair Smith, CEO of Avacta, of work with the organization on a saliva-based COVID test. "This provides better access to a greater number of real samples to validate the tests, which will help speed up the process."

Clinical validation generates the sensitivity and specificity performance parameters used to define the performance of a diagnostic test. LSTM is evaluating the performance of prototype lateral flow tests provided by Cytiva alongside Avacta’s ELISA laboratory test, using SARS-CoV-2 coronavirus samples, as a precursor to full clinical validation studies.

"The main advantage of the antigen test under development with Cytiva is that this [is] a POC test to determine whether you have..."

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TODOS CONTINUED FROM PAGE 24

variety of cancers using a technology that seeks biochemical changes in blood mononuclear cells and plasma of people infected with COVID-19, however, prompted a shift in priorities, leading them to focus on the development of a rapid saliva test for screening for COVID-19 infection.

According to a company news release, the data demonstrate that their assay can accurately detect the SARS-CoV-2 3C-protease in human saliva samples spiked with recombinant 3C protease, and that the protease signal was specifically and significantly distinguishable from background protease activity present in normal saliva. Based on these data, they have initiated a multicenter clinical trial at Assuta Ashdod Hospital and Tel Aviv University in Israel to evaluate the clinical performance of the assay, and optimize product development prototypes for commercial scale-up.

“These data provide proof-of-concept for the 3C-protease diagnostic approach in COVID-19 testing,” said Dr. Jorge Leon of Todos Medical.

“The data provide proof-of-concept for the 3C-protease diagnostic approach in COVID-19 testing,” said Dr. Jorge Leon, consulting chief medical and scientific officer of oncology and infectious disease for Todos. “The clinical trial in Israel will generate real-world data on how best to integrate this technology platform into products that can be deployed worldwide. We will now begin incorporating the software to analyze this assay into an application for use with mobile phones and various telemedicine platforms, so as to provide a more complete and efficient solution for COVID-19 testing and data reporting for all stakeholders.”

The 3C-protease is a coronavirus-derived protein that is required for viral replication and transmission to other cells and tissues. A recently published study in Science Translational Medicine indicated that the X-ray crystal structure of a key protein in the virus’ life cycle is its main protease in instances of COVID-19. That research indicated that “the enzyme cuts the polyproteins translated from viral RNA to yield functional viral proteins.” Building on that knowledge, Todos announced that their 3C-protease assay can detect active SARS-CoV-2 infection, as opposed to a reaction to previous coronavirus infections, or as a response to the lingering biology following a COVID-19 infection. They have already seen millions of people infected with the disease, therefore it is critical to find an assay that detects actively replicating SARS-CoV-2 virus and not remnants of other infections or other diseases.

“We are extremely pleased to have confirmed the usefulness of our 3C-protease patented viral detection technology for COVID-19,” said Dr. Dorit Arad, chief scientific officer of NLC Pharma, a partner with Todos on the research. “With these data in hand, we see a clear path to apply our technology at large scale to provide widespread rapid, highly sensitive molecular testing to make a difference in the rapid detection of active COVID-19. We believe this sets the stage for significant growth within our joint venture with Todos.”

What makes the technology particularly promising is its point-of-care nature and its ease of use. As a saliva-based screening tool, the challenges of sample care, transport and contamination are avoided. This will potentially make the test easy to use in clinical settings, places characterized by high traffic volume—and even at home.

In conjunction with NLC Pharma, Todos has used the first half of 2020 to explore these diagnostic tests that perform distinctly from currently available tests, while also exploring identifiers of how the virus replicates, an indicator of viral load. Todos is working to complete its initial clinical trial in the third quarter of 2020, with trial results and submissions to regulatory agencies worldwide in the fourth quarter of 2020.

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

Both overlapping with and distinct from the main DDNews website, Cancer Research News provides a doorway to news of those making strides in cancer drug development, from individual groundbreaking scientists to big-name companies; a gateway to recent research studies and academic efforts in oncology; and a pathway to find pointed commentaries on issues related to cancer therapeutics and diagnostics.

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Wellcome Sanger updates DECIPHER

Institute also working on genetic prediction of blood diseases and ramping up COVID-19 research

BY LORI LESKO

HINXTON, U.K.—The Wellcome Sanger Institute has updated its DECIPHER program to allow more access to its clinical genomics database, undertaken two genetic studies on how a genetics profile contributes to developing blood diseases and ramped up its research toward finding a treatment for COVID-19.

A new update of its online tool DECIPHER was recently launched by Wellcome researchers and collaborators at Cambridge University Hospitals NHS Foundation Trust (CUH), which runs Addenbrooke’s and the Rosie maternity hospitals, now enables users to input, view and share genomic changes in any region of the genome.

Said to be the largest, most comprehensive resource of its kind in the world, DECIPHER brings together genetic and clinical information from thousands of patients with rare genetic conditions, thus enabling diagnoses for families affected by rare diseases and enhances the understanding of human genetics, according to Wellcome Sanger.

Previously, DECIPHER users could view changes of a single letter of genetic code, and changes in the number of copies of a gene. Now, additional variants are included: regions of repeats-STRs, regions of chromosomes from normal and chromosome variants—including regions inherited in an atypical way.

“After the human genome was sequenced in 2004, we created DECIPHER to put that data to use. Our aim remains the same as when we first launched—to understand the significance of genetic changes in health and disease,” says Helen Firth, a consultant clinical geneticist at Addenbrooke’s Hospital. “DECIPHER, today, continues to bring emerging knowledge of human genetics and genomics to the forefront of clinical practice.”

In DECIPHER, each genetics center maintains control of its own patient data or shares the data with trusted parties in a collaborative group until patient consent is given to allow data, without identifying details, to become freely viewable within genome browsers.

“The first step in finding a cure is finding what the underlying cause of a disease is,” says Prof. Matthew Hurles, head of the Human Genetics division at Wellcome. “Everything is critically dependent on that.” From that point onward, you can narrow in on the particular biology of the disease and what kind of drugs might be needed. Finding the cause of disease in all patients requires comprehensive consideration of all forms of genetic variation, and this latest update to DECIPHER enables exactly this.”

In other news, researchers from Wellcome, the University of Cambridge and colleagues from 101 research institutions worldwide studied hundreds of thousands of participants and identified over 7,000 regions of the human genome that control blood cell characteristics, such as the numbers of red and white cells.

The studies, published in Cell, also show for the first time how a person’s genetic profile contributes to developing blood diseases, bringing us one step closer to using genetic scoring to predict personal risk of developing blood disorders, researchers state.

In addition, Wellcome researchers in August joined national research projects to investigate the role of the immune system in tackling COVID-19.

Three new U.K.-wide studies, bringing together scientists from the Wellcome and 16 other research institutions, will receive £8.4 million from UK Research and Innovation and the National Institute for Health Research to understand immune responses to the pandemic. They will strive to develop better tests to define immunity, to study the body’s immune response to SARS-CoV-2 and to understand why some people suffer from severe life-threatening COVID-19 while others have milde or asymptomatic infections but can still transmit the virus.

DISCOVERING PANCREATIC CANCER EARLIER

Collaborative studies at University of Missouri show promise

BY JENNIFER CLIFFORD

COLUMBIA, Mo.—Earlier this year, the University of Missouri (MU) announced initial results of a collaboration that may help diagnose pancreatic cancer in its earlier, treatable phases. The article, titled “RNA cargos in extracellular vesicles derived from blood serum in pancreas associated conditions,” was published in the journal Scientific Reports.

This interdisciplinary collaboration involving the MU College of Veterinary Medicine and MU School of Medicine helps advance precision medicine, one of the core principles of the NextGen Precision Health Initiative.

“If we can identify the potential for disease development as early as possible, preventative measures can be taken by the patient, which will ultimately lead to improved health outcomes,” said Senthil Kumar, a research professor in the MU College of Veterinary Medicine. “By drawing a blood sample in a minimally invasive manner, we can analyze the nano-carriers called ‘exosomes’ that are present in the bloodstream, which contain different biological information from normal and tumor cells.”

Senthil Kumar of the University of Missouri and surgeons Eric Kimchi and Jussuf Kaifi from MU Health Care’s Ellis Fischel Cancer Center analyzed blood samples from healthy individuals as well as samples from patients at different stages of pancreatic disease.

“These biomarkers early on can help us learn of one’s susceptibility for disease development,” Kumar said. “By drawing a blood sample in a minimally invasive manner, we can analyze the nano-carriers called ‘exosomes’ that are present in the bloodstream, which contain different biological information from normal and tumor cells.”

Symptoms of pancreatic cancer often do not present themselves until after the cancer has progressed, limiting treatment options to invasive procedures such as surgery, chemotherapy or radiation. Even so, current methods of diagnosis only have a small number of useful biomarkers. This system has been used for several years with few significant changes.

Recently, studies have been directed towards identification of biomarkers for cancer and other diseases, through non-invasive means utilizing components in blood such as circulating tumor cells, cell free DNA and very recently extracellular vesicles which includes microvesicles and exosomes.

Through their collaborative studies, MU researchers have identified novel pieces of biological information, such as RNA, which may serve as biomarkers for early detection of pancreatic cancer.

For the initial collaborative study, Kumar and surgeons Eric Kimchi and Jussuf Kaifi from MU Health Care’s Ellis Fischel Cancer Center analyzed blood samples from healthy individuals as well as samples from patients at different stages of pancreatic disease.

“Identifying these biomarkers early on can help us learn of one’s susceptibility for disease development,” Kumar said. “By drawing a blood sample in a minimally invasive manner, we can analyze the nano-carriers called ‘exosomes’ that are present in the bloodstream, which contain different biological information from normal and tumor cells.”

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AVACTA

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the infection right now—so [it] could replace the slower PCR tests that are done on nasal swabs that have to be sent away to labs for testing,” Smith says. “It is different from other rapid tests that detect antibodies in your blood that are raised by your body over a period of a couple of weeks after infection. In the early stages of infection, the antibody tests would not give a positive result, but the Avacta/Cytiva antigen test would.”

“Compared with PCR tests, the test result can be delivered in a few minutes, which means that appropriate actions can be taken immediately as a result: e.g., a patient with a positive sample can isolate themselves immediately reducing potential transmission of the virus,” points out Smith. “A secondary advantage is the cost of the test and the testing process, with this test being much less expensive than laboratory tests and not requiring logistics to transfer samples, or a laboratory to run the test. We intend that ultimately the test will also be available to consumers, which is not really possible for PCR-based tests.”

The Wellcome Sanger Institute is putting genomics to work on rare diseases, hematology, COVID-19 and more.
GlobalData notes in a recent report that India’s contract manufacturing organization (CMO) and pharma market has brought in significant global private equity investments in the past few years. This year alone, the report notes, three such investments totaled $1.2 billion as equity firms acquired stakes in various companies. India boasts the greatest number of public dedicated CMOs with small-molecule API manufacturing facilities, with GlobalData reporting that pharma companies in India are more likely to engage in contract/excess capacity API manufacture than those in other hotspots.

Bhavana Netevena, pharmaceutical analyst at GlobalData, stated, “Over the past three years, India has witnessed growth in private equity investments as a result of relaxations offered by the government, such as increasing the FDI (Foreign direct investment) limit from 49 percent to 74 percent in brownfield pharma ventures. Despite the significant growth in investments, there is still scope for improved pharma regulatory framework in terms of investments and high tax incentives to further attract the investors.”

A bottleneck to hold up ATMP progress?

GlobalData says few CMOs are equipped to manufacture cell and gene therapies

BY JEFFREY BOULEY

LONDON—More than 7,000 cell and gene therapies are progressing through the development pipeline but, according to data and analytics company GlobalData, there are only 152 contract manufacturing organizations (CMOs) that have the capabilities to manufacture them.

The European Medicines Agency (EMA) set aside a whole new category for such products under the Advanced Therapy Medicinal Products (ATMP) category, which encompasses medicinal products for human use that are based on genes, tissues or cells that, as the EMA says, “offer groundbreaking new opportunities for the treatment of disease and injury.”

With its assessment that there aren’t enough CMOs yet to meet demand, GlobalData sees a problem ahead, as this disconnect will become very apparent when more and more ATMPs receive regulatory approval. The lack of enough CMOs will potentially create bottlenecks to large-scale commercial manufacture.

Currently, 79 of those potential cell and gene therapies are for COVID-19, though the majority of these are in preclinical and discovery phases. Two of them are in Phase 3 trials—Merck’s remdesivir-L and Athersys’ Multistem—with another 15 in Phase 2 trials. If these are approved, they will need to be scaled up and manufactured quickly to treat the current pandemic, GlobalData notes.

“There are considerable opportunities for CMOs with the capability to manufacture ATMPs. However, only 152 CMOs have the capability to produce cell or gene therapy APIs for global markets, and of these only 121 are dedicated CMOs,” said Adam Bradbury, a PharmSource analyst at GlobalData.

“Producing gene or cell therapies requires an inherently high level of manufacturing expertise and expensive facility requirements that many pharma companies do not possess.”

Bradbury noted, “With a large number of ATMPs in the drug pipeline greater numbers will be approved. This will require improvements to the production process and the removal of manufacturing bottlenecks to create cost-efficient manufacture at a commercial scale.”

Company expands TriLink BioTechnologies CleanCap capacity and adds new plasmid DNA manufacturing

BY DDN STAFF

SAN DIEGO—Maravi LifeSciences, a global provider of life-sciences reagents and services to researchers and biotech innovators, is expanding its contract development and manufacturing organization (CDMO) capabilities at TriLink BioTechnologies for the second time in less than a year. The expansion is expected to be completed in the first quarter of 2021 and will increase TriLink’s small-molecule manufacturing capacity with a focus on additional scale-up of CleanCap, its proprietary messenger RNA (mRNA) capping technology, for global mRNA vaccine and therapeutic programs. To further address the increasing demand for mRNA development and clinical programs, the company is currently completing the construction of its plasmid DNA production facility as well.

In November 2019, TriLink opened its new headquarters in San Diego and expanded mRNA and small-molecule capacity as it opened five cGMP-certified suites. The current investment will further expand the operation with an additional three cGMP suites and four cGMP manufacturing support suites.

According to the company, the expansion positions TriLink to meet global demand for research- and GMP-grade CleanCap capping reagent, nucleoside triphosphates, and development and cGMP services for mRNA therapeutics and vaccine production. The increase in demand for these critical raw materials and active pharmaceutical ingredients is being driven not only by COVID-19 vaccine development, but also by the rapid growth in investigational mRNA therapeutics and advancements in gene editing and cell therapy such as CRISPR, base editors and CAR-T therapies.

“Biotech startups to large biopharma customers are outsourcing production to specialized CDMOs like TriLink to achieve efficiencies and ensure quality. TriLink’s second expansion provides these innovators with a single qualified and complete production partner for their nucleic acid and small-molecule research and clinical programs,” said Carl Hull, CEO of Maravi LifeSciences.

“Added Brian Neel, chief operating officer of TriLink BioTechnologies: “By integrating plasmid DNA production, TriLink is eliminating the risk of production slowdowns from global supply bottlenecks and streamlining the path to and through clinical trials for our customers. Other measures we’re taking include a move to a 24-hour, seven-day-a-week manufacturing schedule and regular COVID-19 testing of our workforce.”

Maravi expands again to meet mRNA therapy and vaccine demand
Pharmaceutical outsourcing
M&A remains robust
BOSTON—Capstone Headwaters released its “Pharmaceutical Outsourcing” report in mid-August, reporting that despite disruptions related to the COVID-19 pandemic, merger and acquisition (M&A) activity has remained robust in the pharmaceutical outsourcing industry, with 37 transactions announced or completed so far in 2020. This number slightly outpaces the 38 transactions in 2019.

Contract development and manufacturing organizations and lab/testing providers have comprised the majority of acquisitions year to date—at 35.1 percent and 29.7 percent, respectively.

According to Capstone, “The pandemic has emphasized the need for the industry to rethink its reliance on offshore manufacturing and complex global supply chains, as well as how to utilize technology to adopt a more decentralized approach to conducting clinical trials.”

Capitalizing on cytokines
NEW HAVEN, Conn.—Biotechnology company Simcha Therapeutics launched this summer with $25 million from a Series A financing and a focus on developing biologics that modulate cytokine pathways in hopes of better utilizing the immune system. The company’s lead program, which it hopes to move into the clinic in H1 2021, features a customized variant of interleukin-1β that was featured in Nature earlier this year. Simcha’s engineered cytokines are designed to improve immune cell activation, differentiation and proliferation, and to combat immunosuppressive tumor microenvironments.

“At Simcha, we set out to improve on nature’s designs by engineering custom-built proteins that can precisely activate and expand populations of crucial immune responders, such as natural killer cells and T cells. Too many cancer patients do not respond to the immunotherapies available today. We’re hopeful that our approach will provide new options and potential benefits to these patients,” said Dr. Aaron Ring, scientific founder of Simcha and assistant professor of Immunobiology at the Yale School of Medicine.

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Pharma giant acquires Momenta for $6.5B, setting sights on autoantibody-driven disease market
BY KELSEY KAUSTINEN
NEW BRUNSWICK, N.J.—Fall normally signals the end of growth for the year, but that’s not the case for Johnson & Johnson. As summer came to a close, the company announced a definitive agreement under which it will acquire Cambridge, Mass.-based Momenta Pharmaceuticals Inc. in an all-cash transaction that will total approximately $6.5 billion.

Per the terms of the agreement, Vigor Sub Inc. (also known as Merger Sub), a new wholly owned subsidiary of Johnson & Johnson, will commence a tender offer to purchase all of Momenta’s outstanding shares at $52.50 per share. The closing of the offer is subject to the tender of a majority of said outstanding shares to the offer, clearance under the Hart-Scott-Rodino Antitrust Improvements Act and other customary closing conditions. Once the tender offer closes, Johnson & Johnson will acquire any shares not tendered into the offer through a merger of Merger Sub with and into Momenta for the same share price as the tender offer. The transaction is expected to close in the second half of this year. While the acquisition of Momenta provides the Janssen Pharmaceutical Companies of Johnson & Johnson with several benefits—including a bigger stake in the immune disease market and a foothold in the Cambridge biotech hub—the key driver for this deal was nipocalimab, a fully human IgG1 monoclonal antibody. The drug candidate is a potentially best-in-class anti-FcRn antibody that Momenta is advancing in myasthenia gravis, warm autoimmune hemolytic anemia and hemolytic disease of the fetus and newborn. The company shared data in June from a proof-of-concept trial in myasthenia gravis that pointed to strong efficacy, safety and tolerability—52 percent of patients on nipocalimab saw significant reductions in myasthenia gravis Activities of Daily Living (MG-ADL) scores in all four dosing arms, compared to 15 percent of patients in the placebo arm. The trial, Vivacity-MG, is due to be completed in Q3 2020, with 16-week data to be presented in Q4.

“This acquisition broadens Janssen’s leadership in autoimmune diseases and provides us with a major catalyst for sustained growth. Autoantibody-driven diseases are often serious, and patients are underserved by current treatment options,” said Jennifer Taubert, Johnson & Johnson’s executive vice president and worldwide chairman, Pharmaceuticals. “We’re excited by the opportunity to further advance patient care by combining Johnson & Johnson’s extensive experience in research, development and commercialization with Momenta’s highly differentiated product pipeline. Together, we will work to bring nipocalimab—Johnson & Johnson’s first-in-class anti-FcRn antibody—into the market, where it has the potential to improve outcomes in patients with myasthenia gravis.”

J&J seeks immune momentum with Momenta
J&J is acquiring Momenta, in large part because of the latter’s compound nipocalimab, a fully human IgG1 monoclonal antibody.

ON THE CUTTING EDGE
A roundup of instrumentation, software and other tools and technology news
BY JEFFREY BOULEY
LONDON—U.K.-based organizations CPI, MicrofluidX and the Cell and Gene Therapy Catapult (CGTC) announced recently their collaboration in a project to develop bioprocessing technology for the rapid scale-up of cell and gene therapies. The technology has the potential to overcome a major bottleneck in the development of these novel treatments, and reduce the time and costs associated with bringing such therapies to market.

Significant advances have been made in recent years in the use of cell and gene therapies in disease areas with unmet clinical needs. However, reliable methods are still required to scale up the manufacture of these complex technologies to commercial levels, the partners in this collaboration say. Cell and gene therapies are produced from inherently variable living cells. As such, it is highly challenging to achieve consistent performance at different scales, which can lead to prolonged development times. In turn, this can significantly raise the cost of these therapies upon entry to the market.

The microfluidic cell culture technology being developed by MicrofluidX will provide manufacturers of cell and gene therapies with fine process control throughout development, ensuring consistent quality. The technology can be used to optimize cell characteristics and growth conditions early in development, before rapidly transitioning to large-scale manufacturing without the need to invest time in redesigning processes. Crucially, using microfluidics greatly reduces

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the consumption of expensive reagents, cutting down overall development costs. MicrofluidIX recently closed an initial funding round, raising €1.4 million for its microfluidic platform. The company is now working with CPI and CGT Catapult to secure further funding and validate its prototypes.

CPI’s state-of-the-art facilities provide expertise and advanced equipment for developing GMP-compliant bioprocessing technology. In addition, CPI has drawn from its extensive experience in securing public funding to help MicrofluidIX secure £500k of grant funding from Innovate UK for development of the microfluidic bioprocessing platform.

CGT Catapult has more than 200 experts in the industrialization, manufacturing and clinical adoption of cell and gene therapies, and it supports industry and academic partners to develop and commercialize these transformative medicines. In this collaboration, the organization will support MicrofluidIX to implement, test and optimize the microfluidics platform, utilizing the technology and expertise at the CGT Catapult development centre laboratories in London.

For more specific product offerings from some other companies, read on below.

Unlocking deeper discoveries with the $600 genome

SAN DIEGO—Illumina Inc. recently announced the launch of NovaSeq 6000 v1.5 Reagent Kit, which aims to make whole-genome sequencing more accessible and affordable for labs of all sizes with the introduction of the $600 genome.

“In order to explore biology at higher resolution, we rely on technologies that enable us to dive deeper into previously unrecognized cell types with single cell and spatial applications,” said Edwin Hauw, vice president of marketing at 10x Genomics. “Together with Illumina’s technologies, we are able to simplify and amplify our workflows to capture new insights into the inner workings of biology.”

Coupled with the new NovaSeq 6000 v1.5 Reagent Kit, NovaSeq 6000 is said to accelerate scientific breakthroughs with “tremendous flexibility, accuracy and scale—delivering unique, industry-changing capabilities to drive discovery through deep sequencing, access to data-intensive next generation sequencing applications, and sequencing of large sample cohorts—now more affordable than ever.”

Custom service for influenza antigens

OXFORD, U.K.—The Native Antigen Company (now part of LGC’s Clinical Diagnostics Division), a leading supplier of reagents that enables research into vaccines and diagnostics for emerging and endemic infectious diseases, recently announced the introduction of its custom contract service to rapidly develop antigen panels for influenza A and B viruses.

This new service offers scientists access to high-quality proteins from emerging seasonal and pandemic influenza strains, to support ongoing research and development of diagnostics and vaccines.

“The Native Antigen Company provides custom contract services to develop panels of the influenza antigens from a wide range of virus strains and subtypes using its proprietary HEK293 mammalian expression system (VirtuE), which is able to introduce proper protein folding and full glycosylation to closely mimic naturally occurring proteins. “Understanding existing influenza strains and having access to the corresponding antigens is vital to help distinguish infection from that of other respiratory diseases, and to enable accurate diagnosis and treatment,” said Dr. Andy Lane, commercial director for The Native Antigen Company.

Choosing the right HPLC columns and skids for peptide purification

LYON, France—Novasep, a leading supplier of services and technologies for the life-sciences industry, announced that Frontier Biotechnologies Inc. has chosen Novasep Prochrom HPLC chromatography columns and skids for its site in Nanjing, China. Frontier Biotech is a global bio-pharmaceutical company whose core competence is to develop novel antiviral and long-acting drug products, and its first commercial product is Aikening.

“Aikening is effective against most HIV-1 strains, including drug-resistant strains, administered by intravenous infusion on a weekly basis. It is a peptide drug with a good safety profile and no predictable drug-drug interactions,” said Dr. C.J. Wang, CEO of Frontier Biotech. “Because the products and the production stability are closely related to the stability and robustness of the equipment, we hope we can produce Aikening API with highest quality with Novasep Prochrom equipment and meet the requirements of domestic and foreign markets, giving patients the best quality service.”
By Mel J. Yeates

ERK signaling has been a well-known target for researchers focused on oncology. Now, researchers are figuring out how to use the ERK pathway in other ways.

Recently, DDN spoke with Dr. Michael Snape, chief scientific officer of AMO Pharma, to discuss drugs that target the ERK signaling cascade, and how these drugs might be able to treat a range of developmental disorders (e.g., congenital myotonic dystrophy and Rett syndrome).

DDN magazine: How did researchers discover that the ERK signaling cascade could have applications with developmental disorders?

Dr. Michael Snape: Research in this area began in a number of laboratories, mainly in the U.S. in the mid-2000s, with peer-reviewed studies on the ERK signaling cascade published around 2008. Researchers were driven by an interest in how the brain processes and eventually recognizes the biochemical basis for information processing and eventually recognized the fundamental unit of change that captures new information in the brain during development.

Researchers investigated the signaling pathways within brain cells to try to determine the biochemical basis for information processing and eventually recognized the ERK signaling cascade as an important player in the regulation of plastic changes in synapses. Developmental disorders by definition involve a change in the way information is processed in the brain during development. It therefore made sense to investigate the role of systems involved in synaptic plasticity, such as the ERK pathway in developmental disorders.

Prior research efforts have focused on the role of the ERK pathway in developmental disorders including fragile X syndrome and autism spectrum disorders, two areas of interest for AMO, and the results were clear—in brain tissue of patients with these disorders the ERK pathway was aberrantly activated, including the glial cells that support neuronal function. Based on these and other study results, our team recognized the potential of the ERK pathway in the treatment of developmental disorders that currently have no approved treatment options.

DDN: Can you tell us about the clinical studies currently underway for AMO-01?

Snape: As mentioned, we are currently supporting a Phase 2 clinical study of AMO-01 in Phelan-McDermid syndrome being led by researchers at Mount Sinai School of Medicine in New York and Texas Children’s Hospital in Houston. These centers are world leaders in research in Phelan-McDermid syndrome, so this is a marvelous opportunity for AMO to further investigate AMO-01 as a potential treatment for this disorder.

DDN: What other developmental disorders might AMO Pharma be able to target via the ERK pathway?

Snape: There are a number of other developmental disorders characterized by increased Ras-ERK pathway activation—these are referred to as “Rasopathies” and are a recognized group of disorders. We also believe that there are more developmental disorders that involve this pathway than have been previously recognized. Prior research showed that a number of outcome measures that assess the potential clinical impact of Ras activity could be impacted by increased Ras activity. Our team is currently designing a preclinical program to determine the potential of this approach to target some of these disorders and is supporting a Phase 2 clinical study in Phelan-McDermid syndrome.

Our team at AMO has known about the Ras-ERK pathway for several years and learned of its potential in developmental disorders characterized by increased activity of the Ras-ERK pathway, and Phelan-McDermid syndrome and fragile X syndrome are just two. AMO and our collaborators initially prioritized these two conditions based on our prior knowledge and experience with them, and our connections with leading experts in clinical research in these conditions.

Data to date show the same AMO-01 profile in preclinical efficacy studies for both of these conditions—that is, a broad efficacy profile with essentially the same activity profile across both disorders. The potential benefits of AMO-01 persisted for hours, even five to 10 days later, following a single dose in the mouse model of fragile X syndrome.

Other academic groups have also shown that inhibition of the Ras-ERK pathway provides semi-persistent efficacy in similar experimental models of fragile X syndrome. In-vitro and in-vivo testing using knock-out mouse models has also shown that AMO-01 could normalize synaptic abnormalities seen in neurons in fragile X syndrome, underpinning an effect on the underlying biology of this disorder.

Taken together, these findings make our team excited to investigate the potential of AMO-01 to treat fragile X syndrome in the clinic. This is a route our team will consider once we have the safety and efficacy data from the ongoing Phelan-McDermid syndrome study.

DDN: What potential effect might more clinical data from the ongoing Phase 2 clinical trial of AMO-01 add to the research on AMO-01?

Snape: We are excited to see whether the semi-persistent efficacy seen in preclinical studies translates into the clinic. We will also evaluate the safety profile of AMO-01 using a number of outcome measures to assess the impact of AMO-01 on the Ras-ERK pathway in the mouse model of fragile X syndrome.

Encouraged by these findings, AMO is supporting a Phase 2 clinical study in Phelan-McDermid syndrome being conducted at Mount Sinai School of Medicine in New York and Texas Children’s Hospital in Houston. These centers are world leaders in research in Phelan-McDermid syndrome, so this is a marvelous opportunity for AMO to further investigate AMO-01 as a potential treatment for this disorder.

DDN: What are the potential effects of the Ras-ERK pathway on the brain?

Snape: The Ras-ERK pathway is a key regulator of cell growth and proliferation and is involved in a number of cellular processes, including cell survival, proliferation, differentiation, and migration. In the brain, the Ras-ERK pathway plays a crucial role in synaptic plasticity, which is the ability of the brain to adapt and change in response to new experiences.

The potential impact of the Ras-ERK pathway on the brain is significant. For example, inhibition of the Ras-ERK pathway in the brain can lead to changes in the strength of connections between neurons, which is known as synaptic plasticity. This can have important implications for a variety of neurological disorders, including developmental disorders such as fragile X syndrome, autism spectrum disorder, and Rett syndrome.

Our team is actively investigating the potential of the Ras-ERK pathway in developmental disorders characterized by increased activity of the Ras-ERK pathway, and Phelan-McDermid syndrome and fragile X syndrome are just two. AMO and our collaborators initially prioritized these two conditions based on our prior knowledge and experience with them, and our connections with leading experts in clinical research in these conditions.

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LONDON—CPI has signed partnership agreements with Siemens plc, Perceptive Engineering LTD and Process Systems Enterprise (PSE), making them a part of the Medicines Manufacturing Innovation Centre collaboration, which also involves AstraZeneca, Glaxo-SmithKline (GSK) and others.

The partnership agreements are intended to help strengthen the United Kingdom’s position as a global leader in pharmaceutical manufacturing through the development of continuous manufacturing innovations. Each partner will contribute to the development of a digital manufacturing solution, which will help the pharmaceutical industry as it moves towards smaller batches of more personalized medicines that require faster and more efficient manufacture.

Siemens is a global leader in process automation and will provide both hardware and software to enhance the control of pharmaceutical manufacturing processes. The application of Siemens’ leading-edge digitalization technologies will connect the physical and digital worlds and provide the real-time information necessary for rapid decision-making in a secure manner.

Innovation partner Perceptive Engineering will utilize its fully integrated software platform, PharmaMV, to enable the generation of Advanced Process Control models for optimized continuous manufacturing. Rather than simply reacting to a set of data points for in-process control, the PharmaMV platform adapts manufacturing process parameters in response to predictions, ensuring tighter manufacturing specifications can be achieved and quality information is generated in real-time. These approaches also enable the future application of technologies such as machine learning and artificial intelligence to pharmaceutical processing.

PSE is the leading supplier of advanced process modeling (APM) software and will utilize predictive process modeling to increase R&D efficiency, reduce tech transfer risk and develop more robust control strategies. Through use of mechanistic models for continuous drug manufacture in PSE’s gPROMS Formulator®Products platform, the industry is expected to be able to move away from a design-make-test cycle and toward a “predict first” model (i.e. design, test, make). By reordering the R&D paradigm, more design activities can be undertaken before committing material, which will result in fast, sustainable and cost-effective manufacturing process development.

The Medicines Manufacturing Innovation Centre is a collaboration between CPI, the University of Strathclyde and founding industry partners GSK and AstraZeneca, with funding provided by Scottish Enterprise and UK Research and Innovation.

“We are delighted to be part of such a forward-thinking, innovative collaboration with Perceptive Engineering, PSE and the Medicines Manufacturing Innovation Centre,” said Mark Higham, general manager of process automation at Siemens Digital Industries GB & Ireland. “We look forward to unlocking the power of digitalization to achieve continuous improvement and efficiency in pharmaceutical manufacturing in the U.K.”

Added Dave Lovett, managing director of Perceptive Engineering: “We are honored to have been asked to play a part in this groundbreaking initiative. Building on our experience with research organizations and industry leaders worldwide, we are excited to be working collaboratively with CPI at the new Centre. We look forward to helping design and build the next generation of innovative manufacturing technologies for the production of pharmaceutical therapeutics.”

Sean Bermingham, head of formulated products at PSE, noted that the initiative is aimed at publicly demonstrating the benefits that digital design and digital operation approaches can bring to development and operation of continuous drug manufacture processes, and added that “the Medicines Manufacturing Innovation Centre ecosystem is uniquely positioned to successfully achieve this, facilitate knowledge transfer to industry and ultimately bring the associated benefits to patients.”

MilliporeSigma expands ADC manufacturing

BURLINGTON, Mass.—MilliporeSigma in early September announced a $65-million expansion of its high-potency active pharmaceutical ingredient (HPAPI) and antibody-drug conjugate (ADC) manufacturing capabilities and capacity at its facility near Madison, Wis. This investment will, the company says, allow large-scale manufacturing of increasingly potent compounds that have the potential to treat cancer. Completion is expected by mid-2022 and should add approximately 50 full-time jobs dedicated HPAPI manufacturing facilities specifically designed to handle single-digit nanogram occupational exposure limit materials. The facility will incorporate containment areas to produce next-generation linker and payload materials for ADCs. The project is an addition to the company’s Madison campus, which was the first commercial ADC facility in North America designed to handle highly active materials. It will join MilliporeSigma’s established campus in St. Louis, which specializes in ADC bio-conjugation, active pharmaceutical ingredients, excipient and adjuvants manufacturing.

There are now only nine ADCs approved globally. However, the ADC industry is delivering strong growth and is expected to reach $15 billion by 2030, according to MilliporeSigma. While ADCs can provide many benefits compared with other therapeutic options, they also present a unique set of challenges. Their development is complex, necessitating stringent containment infrastructure, and their structural exceptionalism required expertise in a number of different technologies for small and large molecules, as well as analytical capabilities. Due to these challenges, more than 70 percent of ADC projects are outsourced to contract development and manufacturing organizations.

Antibody-drug conjugates are a major part of the focus of a newly expanded manufacturing capability in MilliporeSigma’s Wisconsin facility, starting in 2021.

“ADCs have posted incredible growth over the last decade, and regulatory agencies’ approvals in recent years demonstrate their promise as a targeted therapy,” said Andrew Bulpin, head of Process Solutions at MilliporeSigma. “With more than 35 years of experience in this space, we have been a frontrunner in the development and manufacturing of biologics, conjugation processes and small molecules. This investment underscores our commitment to working with innovators to bring new treatments to patients quickly and more efficiently.”

MilliporeSigma’s new 70,000-square-foot commercial building will be one of the largest dedicated HPAPI manufacturing facilities designed to handle single-digit nanogram occupational exposure limit materials. The facility will incorporate containment areas to produce next-generation linker and payload materials for ADCs. The project is an addition to the company’s Madison campus, which was the first commercial ADC facility in North America designed to handle highly active materials. It will join MilliporeSigma’s established campus in St. Louis, which specializes in ADC bio-conjugation, active pharmaceutical ingredients, excipient and adjuvants manufacturing.

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