**SYBODIES ON THE SCENE**

leadXpro and University of Zurich collaboration to generate membrane protein target-directed sybodies

**BY MEL J. YEATES**

VILLIGEN, Switzerland—In early June, leadXpro and the University of Zurich (UZH) announced a collaboration to generate sybodies as molecular discovery tools, therapeutic lead compounds and diagnostic reagents against disease-relevant membrane protein targets.

Membrane proteins such as transporters, ion channels and GPCRs are therapeutic targets for highly successful medicines. leadXpro’s expertise lies in the generation of membrane protein samples for biophysical analysis and structural investigation by X-ray crystallography and cryo-electron microscopy, and the company generates and applies such samples to the discovery and optimization of small-molecule and biotherapeutic lead compounds. The intent is to extend drug discovery options for previously intractable or challenging membrane protein drug targets.

According to Michael Hennig, CEO and chairman of the board of leadXpro, “leadXpro is located in a region with excellent research facilities like the ETH institutes (PSI, ETH Zurich) and Universities of Basel and Zurich. Prof. Markus Seeger and I have known each other for many years, and we had previous collaborations already. I approached Markus three years ago to use sybodies as chaperones in crystallization experiments for X-ray structure determination.”

The expertise of leadXpro is in generating membrane protein samples for biophysical analysis and structural investigation by X-ray crystallography and cryo-electron microscopy—the company generates and applies such samples to the discovery and optimization of small-molecule and biotherapeutic lead compounds.

**Cracking the code**

Scripps uncovers new transcription factor combos to reprogram skin cells into different neurons

**BY KELSEY KAUSTINEN**

LA JOLLA, Calif.—In the latest advance for cellular reprogramming technology, a team of researchers from The Scripps Research Institute have reported on the discovery of several new transcription codes for differentiating skin cells into multiple different types of neurons. Their work, detailed in a paper titled “Diverse reprogramming codes for neuronal identity,” was published in Nature.

**THE WAR AGAINST RESISTANCE ADVANCES**

U.K. and FIND team up to combat global threat of antimicrobial resistance

**BY JEFFREY BOULEY**

LONDON & GENEVA—The 71st World Health Assembly, held recently in Switzerland, served as the venue for a side event at which an important announcement was made: the signing of a memorandum of understanding (MOU) that establishes a three-year project focusing on connecting vital data from patients’ diagnostic test results to national antimicrobial resistance (AMR) surveillance programs in low- and middle-income countries (LMICs). The goal: to help combat the growing threat of drug-resistant infections.

More specifically, it was the U.K. government’s Global Antimicrobial Resistance Innovation Fund (GAMRIF)—part of the Department of Health and Social Care—and the Foundation for Innovative New Diagnostics (FIND) that signed the MOU on connectivity for diagnostics that can combat AMR.

To improve worldwide surveillance of AMR, FIND and its partners will develop tools and solutions to connect vital information from AMR-related diagnostic testing of patients and ensure it reaches national surveillance programs in LMICs, extending their scope to include routine hospital and community data.

Some 700,000 global deaths each year are estimated to be caused by drug-resistant AMR.
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GlobalData: Immune-based gene therapy candidates should prevail in oncology

LONDON—Gene therapy combines a reduced treatment duration with a higher chance of cure, unlike conventional oncology treatments such as chemotherapy. However, this novel therapeutic approach requires the delivery of genetic material to the patient, an uncharted territory in oncology which will necessitate the implementation of new regulatory guidelines and the restructuring of existing treatment algorithms in various oncology indications, notes data and analytics company GlobalData.

The company’s recent report, “Gene Therapy in Oncology” covers the competitive landscape of gene therapies in oncology and the regulatory framework concerning their clinical development and commercialization across the eight major markets (United States, France, Germany, Italy, Spain, United Kingdom, Japan and China), looking in detail at the Phase 3 and Phase 2 cancer gene therapy candidates that are expected to enter the oncology space within the next decade.

According to GlobalData, the current clinical development of gene therapies in oncology is dominated by smaller biotech and pharmaceutical companies—AstraZeneca, Volkan Gunduz, an analyst at GlobalData.

UP AND COMING
Financing news from young and emerging companies in pharma and biotech

BY DDNEWS STAFF
SAN DIEGO—Leading off our financing news roundup this issue is Metacrine Inc., a biotechnology company developing therapies to benefit patients with liver, gastrointestinal and metabolic diseases, which recently completed a Series C financing that raised $65 million in new funds. The investment was led by Venrock Healthcare Partners and includes new investors Franklin Templeton Investments, Deerfield Management, Arrowmark Partners, Invus, Lilly Asia Ventures, Vivo Capital and other undisclosed investors. Existing investors Arch Venture Partners, venBio, Polaris Partners, NEA and Alexandria Venture Investments participated in the financing as well.

Founded in 2015, Metacrine has now raised a total of $125 million in equity financing. According to the company, since inception it has leveraged its highly experienced internal team in biology, chemistry and protein engineering to discover and develop novel therapies and has “judiciously expanded” its capabilities to include early development, clinical and regulatory expertise. With these capabilities, Metacrine says it has built the

FINANCE CONTINUED ON PAGE 5

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Spring cleaning
A roundup of recent GlobalData prognostications on specific therapeutic markets

BY DONNEWS STAFF

ONE OF THE CHALLENGES at times is keeping up with the various pieces of market news in this magazine with only one small section in which to highlight them. But with a larger-than-normal section this issue to play with, we thought we’d do a little “spring cleaning” (even if it is early summer) and share some spring predictions from data and analytics firm GlobalData that have long-term implications.

OSTEOPOROSIS MARKET WILL GROW TO $11.2B BY 2027

Despite being dominated by generic bisphosphonates, the osteoporosis market is likely to undergo significant changes over the next 10 years, growing at a compound annual growth rate (CAGR) of 4.3 percent and reaching $11.2 billion by 2027, according to GlobalData. The launch of two key products will diversify physicians’ anabolic arsenal, moving the use of these bone-forming agents up the treatment paradigm. The impact of these agents has already been noted with the launch of Radius Health’s Tymlos in the United States last year.

Despite current setbacks with the FDA related to potential cardiovascular adverse events, Amgen’s novel sclerostin inhibitor, Evsyx, is forecast to enter the United States and other markets from 2019 onwards. It will offer a much-needed alternative therapy with a more appealing once-monthly dosing regimen, novel mechanism of action and strong efficacy profile. Evsyx is forecast to become the leading branded product in the market by 2027, commanding a 17 percent market share.

“We expect uptake of these new anabolic agents to be strongest in more severe patients who have or are considered at high risk of developing a fracture,” said Alice Stevens, a healthcare analyst at GlobalData. “For many years the only anabolic therapy on the market has been Forteo, which due to its high price tag has been restricted to the later lines of therapy and more severe patients. However, the diversification of the anabolic offering is likely to increase competition within this space, driving down prices and potentially bolstering the use of these therapies up the treatment paradigm.”

“The arrival of the new anabolic therapies, and biosimilars to current market-leading branded products, are likely to shape the osteoporosis market over the next 10 years, potentially moving treatment paradigms away from standard generic bisphosphonate therapies.”

AMD MARKET WILL ROCKET TO $11.5B BY 2026

Pharmaceutical sales within the age-related macular degeneration (AMD) market were estimated to be $4.9 billion across the seven major markets (United States, France, Germany, Italy, Spain, United Kingdom and Japan) in 2016. This is expected to reach $11.5 billion in 2026, with an impressive CAGR of 8.9 percent, according to GlobalData. The company states that this growth will be driven by new therapies entering the market and a global aging society, which will lead to increasing numbers of elderly people developing AMD.

GlobalData predicts the launches of three drugs for the treatment of geographic atrophy (GA), the late stage of dry age-related macular degeneration (dAMD), and three late-stage pipeline drugs for wet AMD (wAMD) coming online. In particular, the launch of drugs into the AMD market to treat dAMD will be a larger driver of growth, as there are currently no prescription medications available for these patients.

“We expect that with the launch of brocilizumab in the wAMD market, Novartis will offset the losses to Eylea and regain dominance in the AMD market,” said Dr. Edit Kovacsik, a healthcare analyst at GlobalData. “Once more efficacy and safety data accumulates and physicians become more accustomed to the use of brocilizumab, its advantage of less-frequent dosing will allow it to claim an increasing share and become a first-line therapy if reimbursed.”

New drugs entering the dAMD market will include two anti-complement agents—Apellis’ APL-2 and Ophthotech’s Zimura—and one neuroprotective agent: Allergan’s Brimol DDS, which together will drive an increase of the treated AMD cases, expanding the AMD market.

Kovacsik adds: “Following the failure of both Phase 3 trials of lamalizumab for the treatment of GA, Apellis’ APL-2 emerged as the most promising GA drug after its positive Phase 2a results were announced. Provided that the planned Phase 3 trial of APL-2 for GA will confirm these results, we forecast that Apellis’ drug will reach blockbuster status within a few years of its launch, by 2025.”

OBESITY MARKET PROVING TO BE A CHALLENGE TO PENETRATE

The obesity market may not be the mega-blockbuster market some were predicting, according to GlobalData. The latest bankruptcy filing by Orexigen Therapeutics, whose Contrave proved a disappointment, shows how hard it is to enter this potentially lucrative market, the firm notes, and despite the obesity epidemic, Vivus’ Qymnia and Arena Pharmaceuticals’ Belviq, two other once-promising drugs, also failed.

One question is why this market is so severely skewed towards the early-stage pipeline, given the failure of these drugs. According to GlobalData’s Pharma Intelligence Center, there are two drugs in Phase 3, 17 in Phase 2 and 33 in Phase 1. Novo Nordisk, Eli Lilly, Amgen, Boehringer Ingelheim, Johnson & Johnson, AstraZeneca, Sanofi and Novartis all have early-stage assets in this space. Particularly active is Novo Nordisk, with one asset in Phase 2 and six in Phase 1. It successfully repurposed one of its type 2 diabetes (T2D) drugs, Victozza, into an anti-obesity pill with a new brand name: Saxenda. Novo Nordisk is already dominating the T2D space, as not only are many T2D patients obese, but also most obese patients are at high risk of getting T2D. Novo Nordisk found a way of entering this space without risking much. Its Phase II asset for obesity, semaglutide, is also a T2D drug and shows weight loss effects on top of its glycemic benefits.

“The early-stage assets show a variety of novel mechanisms of action, so there is hope that science has come up with ways of tackling obesity that are ingenious enough to convince big pharma players to develop these assets despite the failings of the last three drugs,” said Dr. Valentina Ghrucik, director of cardiovascular and metabolic disorders at GlobalData.

U.S. DOMINATES BIOSIMILARS MARKET, BUT BRAZIL AND SOUTH KOREA ARE GAINING

Biosimilars are becoming increasingly popular with pharmaceutical companies; however, knowing which markets have been saturated with biosimilars and which are open remains an important consideration for pharma companies, observes GlobalData.

“The deal activity can provide a useful indication of which biosimilar drugs are in development. The recent strategic alliances show the potential of bringing these biosimilar monoclonal antibodies to market for therapy areas such as cancer or autoimmune diseases,” noted Lisa Marris, a healthcare analyst at GlobalData, adding that emerging markets such as Brazil and South Korea have been involved in a growing number of deals for the development or commercialization of biosimilars, thus gaining a foothold for these countries in the future of the biosimilar market.

The countries with the highest deal values and highest number of deals in the past five years reveals that the U.S. continues to dominate biosimilar activity, with the highest total deal value and highest percentage of deals for an individual country. The European Union as a whole has a larger proportion of deals compared to the United States, and these are predominately made up of Germany and the United Kingdom. Brazil and South Korea are also active in the biosimilar market, as noted earlier. “The arrival of the new anabolic therapies, and biosimilars to current market-leading branded products, are likely to shape the osteoporosis market over the next 10 years, potentially moving treatment paradigms away from standard generic bisphosphonate therapies.”

Alice Stevens, an analyst at GlobalData
PACE OF PHARMA INNOVATION ACCELERATES

Record number of new blockbuster drugs forecast to hit the market in 2018

PHILADELPHIA—Clarivate Analytics announced recently the launch of its annual “Drugs to Watch” report. The analysis identified 12 new drugs forecast to achieve annual sales of $1 billion or more (blockbuster status) by 2022 using the Cortellis database, which includes information gathered from diverse sources including drug pipelines, patents, clinical trials, chemistry, deals and company announcements. More blockbuster drugs have been predicted to launch in 2018 than in any other year since the “Drugs to Watch” report began in 2013.

“Despite political and regulatory uncertainties in the USA and EU markets, the annual ‘Drugs to Watch’ report 2018 shows that the pace of pharmaceutical innovation continues to accelerate,” explained Mukhtar Ahmed, president of life sciences at Clarivate Analytics. “2018 is on track to see many more potential gene-changing drugs to market, which will benefit the lives of millions of patients around the world.”

The full report is available at: http://info.clarivate.com/drugstowatch2018

FINANCE

CONTINUED FROM PAGE 3

infrastructure to advance potential best-in-class novel medicines from discovery through to full clinical development.

“The team at Metacrine has repeatedly proven to be scientifically driven, highly productive and very creative,” said Dr. Rich Heyman, chairman of Metacrine. “We are very pleased to have a leading syndicate of investors to partner with the company to build a lasting enterprise that aims to develop drugs than can materially benefit patients.”

Metacrine’s lead program is focused on the farnesoid X receptor (FXR). FXR represents a promising target to treat non-alcoholic steatohepatitis (NASH), a debilitating condition that is becoming a leading cause for liver transplant and for which no approved therapies exist today. In addition to NASH, Metacrine has identified a potential role for FXR in diarrheoa-predominant irritable bowel syndrome (IBS-D) and inflammatory bowel disease such as Crohn’s disease and ulcerative colitis.

Through Metacrine’s discovery efforts and extensive characterization of a broad set of FXR agonists, MET409 has been selected as the lead clinical candidate. MET409 is a novel acid FXR agonist and has demonstrated robust preclinical efficacy with a predicted favorable safety profile. While there are a number of FXR agonists in development, Metacrine believes it has identified key factors in regards to FXR engagement that are important for efficacy as well as safety.

Rain flows through $18M Series A

FREMONT, Calif.—Rain Therapeutics Inc., a privately held, clinical-stage biotechnology company focused on biomarker-driven, small molecule therapeutics for patients with cancer, in May announced the closing of a tranches Series A financing of $18.4 million and emerged from stealth mode. The financ-

ing was led by San Francisco-based Biotechology Value Fund (BVF) and followed by Perceptive Advisors, Auckland UniServices Limited’s Investors Fund and other private investors. BVF’s Dr. Gordan Hrustanovic will join the Rain board of directors in conjunc-

tion with the financing. The Series A round follows a $1.1-million convertible note financ-

ing completed late last year.

“With the proceeds from recent financings, we can complete a Phase 2 proof-of-concept study and continue to advance talrotxinib,” said Avanish Vellanki, Rain’s co-founder and CEO. “Our goal is to provide Exon 20 patients with a novel treatment option that results in significantly increasing the diversity and affordability of novel treatments for cancer and other unmet diseases.”

Using its platform, PhoreMost has built a proprietary novel target pipeline, signed two pharma collaboration deals and spun out a new company, NeoPhore, to progress a novel target into the small-molecule development stage. The funding will enable PhoreMost to expand the range and depth of other proprietary targets into the drug discovery process.

HiFiBiO secures $37.5 million in Series B

CAMBRIDGE, Mass., HANGZHOU, China & PARIS—May saw HiFiBiO Therapeutics, a company focused on the discovery of therapeutically antibodies through single-B-cell screening and analysis, announce the completion of a $37.5 million Series B financing round and the company’s transformation into “a multinational biopharmaceutical enter-

prise with an experienced management team, stronger global presence and rich pipe-

line of novel antibody drugs to treat cancer and autoimmune disorders.”

“With our oversubscribed Series B fund-

ing, expanded drug development team and new facilities on three continents, HiFiBiO Therapeutics is now poised to generate breakthrough immune modulators to address unmet medical needs around the world,” said HiFiBiO Therapeutics President and CEO Dr. Liuang Schweizer. “Our significant pipeline progression is supported by our leadership’s commitment to open innovation generating new biological insights from multiple collabor-

ations with leading global academic insti-

tutions and biopharmaceutical companies.”

Zomedica announces private offering

ANN ARBOR, Mich.—Zomedica Pharmaceu-
ticals Corp., a veterinary diagnostic and phar-

maceutical company, announced recently the commencement of a private offering of its common shares, without par value. To that point, the company had sold an aggregate of 255,815 common shares for gross proceeds of $550,000 in the offering. All of the common shares sold in the offering were subject to a statute­four-month hold period in accordance with applicable Canadian securities laws, which will expire on Sept. 16, 2018.

The common shares had not been regis-
tered under the Securities Act and were not able to be offered or sold in the United States absent registration or an applicable exemp-
tion from such registration requirements. 

IMMUNE

CONTINUED FROM PAGE 3

is the only large pharmaceutical company with an in-house gene therapy in late-stage clinical development. Other major play-

ers, such as Johnson & Johnson, have the exclusive worldwide rights to develop other companies’ products.

Viral gene therapies dominate the late-stage pipeline, with 25 gene therapy candidates in clinical development in a variety of oncology indications. The most commonly targeted tumor types include melanoma, which is highly responsive to immunotherapies, and prostate cancer.

Oligonucleotide and viral gene thera-
pies dominate the Phase 3 pipeline, while oncolytic viral gene therapies are more commonly represented in the Phase 2 pipeline. In contrast, there is limited clin-

ical development of other types of gene therapies such as bacterial gene therapies and transgenes.

“Ampole opportunity remains in the oncology space for gene therapies. One of the most promising therapeutic strate-
gies is developing combination regimens of genes with immune check-

point inhibitors,” said Volkan Gunduz, senior oncology and hematology analyst at GlobalData. “In this end, significant opportunity exists, as half of the Phase 3 pipeline is evaluated as a monotherapy and only one candidate is evaluated in combination with a checkpoint inhibitor.”

According to GlobalData, the use of novel cancer gene therapies in combina-
tion with immune checkpoint inhibitors will provide more clinical benefit to can-

cer patients, increasing treatment dura-

tions significantly. The high cost of novel therapies and longer treatment durations are major factors that will increase the cost of care in the oncology space. 

For more information, visit www.DDN-News.com
LOS ANGELES—Vitality Biopharma Inc. has reported new findings detailing the antimicrobial activity of cannabinoids and their potential for treating C. difficile-associated diarrhea and colitis. Vitality has demonstrated that cannabinoids including THC can serve as effective antibiotics for C. difficile, vancomycin-resistant Enterococci and other pathogens. The company has submitted a patent application for related intellectual property and plans to evaluate VBX-100—a proprietary gas-transient-targeted THC compound—as a treatment for C. difficile-associated diarrhea and colitis. Dr. Brandon Zipp, Vitality’s Director of R&D, commented that “Our recent studies show that cannabinoids may be useful for both addressing the inflammatory state of the colon, as well as confronting the microbial dysbiosis at the root of the problem.”

Kv1.3 ion channel blocker shows potential in rare disease

SEATTLE—Kv1.3 Therapeutics Inc. shared data at the recent American Academy of Neurology Meeting from sporadic inclusion body myositis patients (sIBM) showing high expression of the Kv1.3 ion channel on lymphocytes from their skeletal muscle biopsies. Kv1.3 is often found on T effector memory cells, which play a role in several T cell-mediated autoimmune disorders. The presence of this ion channel on lymphocytes in this patient population supports the use of Kv1.3 Therapeutics’ dalazatide as a potential treatment for sIBM. Dalazatide is a highly selective and near-toxic Kv1.3 ion channel blocker with a track record of producing a series of viable candidates. The collaboration is dedicated to delivering tailored solutions for clients and a more personalized service ranging from target evaluation to candidate nomination and predicted clinical pharmacokinetics and dose.=XenoGesis—a provider of DMPK services, quantitative bioanalysis, in-vitro pharmacology, modeling and simulation for human pharmacokinetic and dose prediction—has a history of delivery in drug discovery. The company’s laboratory tests build a full picture of the ADME properties of a molecule, including required human drug exposure, backed up with advice on how to modify the chemical structure of a compound to make it more “drug-like.”

BioAscent and XenoGesis combine core capabilities

NEWHOUSE & NOTTINGHAM, U.K.—BioAscent Discovery is collaborating with XenoGesis to offer an enhanced range of integrated drug discovery services, including medicinal chemistry, biology and drug metabolism and pharmacokinetics (DMPK). Both companies also have a track record of producing a series of viable candidates. The collaboration is dedicated to delivering tailored solutions for clients and a more personalized service ranging from target evaluation to candidate nomination and predicted clinical pharmacokinetics and dose.

AiCuris, Max Planck Institute look to natural products for new weapons against viral, bacterial infections

WUPPERTAL & DORTMUND, Germany—Antibiotic resistance is one of the biggest and most pressing health issues today, both in the United States and worldwide. While some antibiotic resistance is a natural occurrence—vulnerable bacteria are killed by antibiotics, while resistant strains survive to reproduce, making them the predominant forms—it is exacerbated these days due to factors such as international travel and the overprescription of antibiotics. While the problem has been around for a while now, many have noted that too few pharma and biotechs seem willing to step up to it. The U.S. Centers for Disease Control and Prevention (CDC) estimates that in up to 50 percent of cases, antibiotics are not optimally prescribed or prescribed when not needed. According to the CDC, some two million illnesses and 23,000 deaths are attributed to antibiotic resistance, with a majority of infections and deaths under fire
pounds in screening-ready format.

XenoGesis and BioAscent have both received investment from BioCity Group and are based at BioCity Group sites in Nottingham and Glasgow. BioCity Group, a U.K.-based business incubator that supports the growth of ambitious life-sciences businesses, was founded in 2002. It is home to more than 250 businesses across locations in Nottingham, Glasgow and Alderley Park.

According to Paul Smith, CEO of BioAscent, “There is a longstanding connection between BioAscent and XenoGesis, with a deep understanding of each other’s capabilities and how these interrelate. We saw a gap in the market for a focused, tailored service where the providers have genuine expertise in the three key drug discovery disciplines of biosciences, medicinal chemistry and DMPK.”

Richard Weaver, managing director of XenoGesis, added, “Each company sees a benefit to its clients in the collaboration, allowing us together to offer a truly comprehensive integrated drug discovery service. Both companies share an ethos of putting science and the client first, offering high-quality laboratory services with the best impartial advice from our experts. Based on the complementarity of our expertise and our shared cultural values, we expect this collaboration to thrive over time.”

As Smith explained, “Activities are project-specific and tailored for each discovery program, as no two drug discovery programs are alike. Projects might start with (for example) upfront DMPK consultancy advice from the team at XenoGesis or assay development and high-throughput screening from the team at BioAscent. Clients can then place parts or all of their discovery activities with us, secure in the knowledge they have access to a comprehensive but science-driven drug discovery service.”

“Due to our consultative approach, XenoGesis and BioAscent will work closely together to handle account management in a way that suits the specific project requirements. Furthermore, our dedicated client relationship management teams have the systems and processes in place to manage all client projects from start to finish,” Weaver continued. “The focus will always be science-led, bringing together our combined DMPK, medicinal chemistry and biosciences expertise to benefit our clients’ drug discovery projects. Of course, we are also working together on joint business development efforts.”

Both companies describe the commercial potential of the alliance as “huge.” The global drug discovery market is currently valued at $22 billion, with double-digit growth forecast over the next five years. This growth is driven by a trend towards outsourcing with an increasing need for integrated drug discovery services, and the two companies have identified that there is room in the market for a comprehensive, science-driven drug discovery service. They believe that the combination of capabilities and expertise makes the team unique in the market. 

“There is a longstanding connection between BioAscent and XenoGesis, with a deep understanding of each other’s capabilities and how these interrelate,” says Paul Smith, CEO of BioAscent. “We saw a gap in the market for a focused, tailored service where the providers have genuine expertise in the three key drug discovery disciplines of biosciences, medicinal chemistry and DMPK.”
of R&D services, and one of its core strengths is its chemistry capacity, allowing acceleration on chemical synthesis and experimental validation of the molecules generated by Insilico AI from scratch. The companies complemented each other’s capacity, with Insilico doing the work in the digital space while WuXi provided the solid experimental base.

“Insilico has a very strong AI team, but it does not have a group of seasoned drug development or business development professionals in-house,” according to Lennart Lee, a principal venture capital investor at WuXi AppTec. “Alex Zhavoronkov is currently building out the [Insilico] team, and he will need to build the right team of people around him.”

WuXi AppTec’s investment came from its Corporate Venture Fund and was bolstered by several additional financing partners including Pavilion Capital, BOLD Capital Partners and JoveneScience. The joint project represents a significant win for both companies.

“We will significantly accelerate both the AI development and the biology and chemistry efforts and expand the teams at Insilico,” says Dr. Alex Zhavoronkov, founder and CEO of Insilico Medicine. “We will also collaborate with the WuXi’s leading scientists very closely. Currently we are also planning to open a company in China... because an AI company without a substantial R&D presence in China will not be able to lead in the long-term.”

The companies anticipate another round of funding coming forth in the third quarter of 2018, pending the establishment of some new goals and a successful outcome in the preclinical validation exercises.

“WuXi AppTec hopes to use Insilico’s AI technology to predict pharmacological properties of drugs and supplements and identify novel biomarkers. We hope the technology would allow our researchers to generate novel therapeutic candidates, with a focus on aging and age-related diseases,” asserts Lee. “We are hopeful that our partnership will accelerate our drug discovery process.”

“Our team is very dedicated, and if something happens along the way and we fail with one of the experiments, there are always many others in parallel. And our AI pipelines are constantly improving,” says Zhavoronkov. “In the case that we fail in one experiment, we will be able to rapidly re-engineer our AI and do better.”

Adding to the current excitement and promise at Insilico, they have also just been named as a recipient of the North American Technology Innovation Award from Frost & Sullivan, for a product with innovative features and functionality that is gaining rapid market acceptance.

“Technology leadership in artificial intelligence for drug discovery and biopharmaceuticals is gaining rapid market acceptance. There are always many others in parallel. And if we fail in one experiment, we will be able to rapidly re-engineer our AI and do better.”

The Waldmann research group at the Max Planck Institute of Molecular Physiology will investigate and optimize compounds that prove active against bacterial and fungal infections. The concepts developed at MPI Dortmund can pave the way to the discovery of new drugs. The expertise of MPI scientists in chemical biology and drug discovery was noted in a 2018 Technology Innovation Award.

“We will significantly accelerate both the AI development and the biology and chemistry efforts and expand the teams at Insilico,” says Dr. Alex Zhavoronkov, CEO of Insilico Medicine.
Under this research and development collaboration, leadXpro will provide purified membrane protein and UZH will apply their sybody platform, which is unique in generating synthetic single-domain antibodies (dubbed sybodies) against challenging membrane proteins. leadXpro has the option to acquire any resulting commercial applications of the developed products.

“In this challenging project, we apply our recently developed sybody selection platform to enable drug discovery on a disease-relevant membrane protein. As an academic innovator lab, we have a strong interest in making our technology accessible to skilled and experienced industry partners, like leadXpro,” remarked Markus Seeger, project leader and a professor at UZH.

Iwan Zimmermann, co-inventor of the sybody technology, UZH, added, “The project gained quickly momentum, due to the combination of the excellent target quality delivered by leadXpro and our highly efficient sybodies. The collaboration is an excellent validation of our binder technology towards future therapeutic applications.”

Sybodies are synthetic single-domain antibodies that have been developed in the Seeger research group at UZH. “Some animals like camels, llamas and sharks generate so-called nanobodies. They are smaller in size compared to antibodies and can be produced easily,” says Hennig.

According to the research published in eLife, the sybodies are “designed to mimic the natural shape diversity of cameld nanobodies, thus allowing for an optimal surface complementarity and the limited hydrophilic epitopes on membrane proteins. The application of ribosome display for synthetic nanobody libraries allows processing of very large diversities, thus compensating for the incremental antibody maturation taking place in vivo. Our approach permits the selection and preparative production of sybodies within three weeks and requires only standard laboratory materials.”

Sybodies have been engineered for targeting challenging integral membrane proteins and are selected entirely in vitro, thereby enabling rapid binder generation in the presence of non-covalent ligands against delicate targets. Due to their high thermal stabilities and low production costs, sybodies show promise for diagnostic as well as therapeutic applications. Sybodies are ideally suited to trap intrinsically flexible membrane proteins in defined conformational states and thereby facilitate structure determination by X-ray crystallography and cryo-EM.”

Mathieu Botte, senior scientist and project leader at leadXpro, said, “Generation of high-quality membrane protein samples is a core competence of leadXpro’s lead discovery platform. Within only three weeks, our collaboration partners at UZH have successfully generated a highly diverse set of sybodies that are directed against our challenging target protein. Binding properties were characterized with our platform of biophysical methods (e.g. Creoptix’s wave-guided interferometry) and revealed up to pH affinities and favorably slow dissociation rates for several binders. Sybodies are therefore ideal candidates for the formation of stable complexes for structural studies, and they represent excellent therapeutic lead compounds.”

“In addition to employing our membrane protein samples for our structural and biophysical analytical tool set, we can now expand the utility of our samples as antigens for the generation of sybodies or antibodies,” Hennig adds. “While this collaboration is our first entry into the biologics discovery space, benefits from the generated sybodies at stabilization, crystallization and tools to aid our laboratory partners at UZH have useful potential. It will enable structure-based drug discovery for disease mechanisms that have not been identified by these methods to discover new treatment options for patients. In addition, sybodies could be drug molecules themselves, like the many antibody treatments that are currently available,”

The University of Zurich (pictured here) will apply its sybody platform against challenging membrane proteins using purified membrane proteins provided by collaborating company leadXpro.
UNTIL THE MOMENT I sat down to ponder this month’s editorial, I was undecided about using neglect of ovarian cancer as my topic this month, although I had in my queue of potential topics a news release about an Australian oncology researcher, Dr. Jim Coward, who says ovarian cancer patients are losing out as badly needed funds and clinical attention go to other, more ‘prominent’—yet not as deadly—women’s diseases.

Then came the retweet on my Twitter feed, of someone talking about how ovarian cancer often goes undetected because the tendency is to assume women simply need to lose weight, instead of actually considering weight gain and pain as possible symptoms.

Given that my mom died roughly two decades ago in her early 50s of ovarian cancer that went undiagnosed until the very late stages because her physician repeatedly accused her of secret binge-eating when she visited multiple times for unexplained bloating, weight gain and pain—I decided to take that as a sign.

As noted by Coward, an associate professor and oncologist who is leading the clinical trial of the Australian therapy Cantrixil for recurrent ovarian cancer, ovarian cancer treatment lags far behind that of the more publicized breast and cervical cancers.

“More needs to be done in developing novel clinical trials to help enhance the survival rates for women with ovarian cancer,” he said, “but we only really gaining small steps in understanding ovarian cancer—how it evolves, how the tumor behaves over its established, where it origi- nates—and making small gains subsequently in developing effective treatments.”

As a pharma/biotech market journalist and as a compassionate human, I am pleased to see progress on any cancer front, because it means not only new gain and pain—I decided to take that as a sign.

OUT OF ORDER: RIGH NOTTORY?

WHEN FACED with a terminal illness, the last thing anyone wants to hear is that the medical establishment has nothing left in its arsenal to help you. Yet, for so many patients, this is precisely the case, and with no alternatives in front of them, many are tempted to try the unorthodox and the unproven.

To some extent, medical tourism is built on that desperation; the hope that a treatment that has not found domestic approval might yet be worth a try somewhere else. —locations where regulations aren’t as strictly enforced, perhaps.

With the recently signed Right-to-Try legislation, however, these patients might have another option. Rather than spend their remaining few dollars on travel to distant lands, they can spend that money at home, paying out of pocket for experimental therapies on-demand, if those treatments have passed Phase 1 clinical trials.

The patient doesn’t have to enroll in the drug company’s clinical trials to receive therapy, and the results of right-to-treaty will not be used in regulatory review of the treatment for ultimate approval.

If we set aside the cost issue for a moment, this seems like a wonderful opportunity for patients who see the risk of death as more worrisome than the risk of adverse events. And it indemnifies the drug companies from the risk of having their experimental therapeutics tagged with negative outcomes from uses they likely never intended. There is, in other words, another perspective.

In May, I questioned the clinical and scientific utility of single-arm clinical trials, suggesting that with a comparator (e.g., placebo or standard of care), there could be no statistical understanding of the resulting data. A counter-argument for that could be that the sheer numbers of patients achieving similar results suggests that something was happening, and if most of those responses were positive, was that a good thing?

In the more distant past, I also questioned the validity of off-label prescribing of approved drugs. To me, clinicians were holding unregulated clinical trials based on personal prescribing experience with a treatment, clinical hearsay in the form of case studies or logic exercises based on suspected modes of action.

Again, the caution could be that because the treatment has already been approved, even if not for this specific patient population, it has been well characterized through numerous clinical trials and post-marketing monitoring. Thus, the relative risk profile of receiving treatment is largely known and the clinician can make a well-informed decision about the risk to his or her patient.

What is being proposed through Right-To-Try, however, invalidates both counter-arguments.

Rather than offering whatever statistical validity could be gained from sheer numbers of participants, when the patient exercises his or her right-to-try, N = 1. Thus, whatever happens once treatment starts offers essentially zero scientific or clinical insight.

And because treatment is being given with a drug that has likely not been tested on very many people even if it has passed Phase 1 testing, the risk profile is still largely unknown. Just look at the numbers of drugs that fail in Phase 1 or even post-approval due to safety concerns.

Again, I understand that for the patient who is facing death, none of this likely matters.

If the treatment fails, it doesn’t change the patient’s outcome; but if it positively impacts the disease course and extends the patient’s life, it was worth the risks.

All of this should matter, however, to those in the healthcare, drug and allied industries.

Even if these patients are being given Right-To-Try treatments outside of the patient selection processes, should we not still try to learn everything we can from that treatment of that patient?

In choosing to participate in a “clinical trial of one”, should the patient not be expected to participate in the same scientific analysis as patients who enroll in clinical trials of dozens, hundreds or thousands?

If the treatment fails, then perhaps we can learn something that helps us better select other patient populations. If the treatment succeeds, then we may have the basis of future trials and other indications.

But without examining endpoints and biomarkers, without profiling patient –omics, without monitoring metabolic chemistries and adverse events, the failure or success of treat ment stands as completely meaningless to the scientific and clinical communities.

I appreciate what I am assuming would require great clarity on a variety of fronts, not the least of which is corporate and medical liability of having such information. But how is that ultimately different from the clinical trials process as it stands?

The hope of experimentation is to better understand the situation after the experiment than you did before it.

No matter how you parse it, Right-to-Try is an experiment.

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Editor’s focus: Cancer should not be a ‘popularity contest’
COMMENTARY: Improving results after hematopoietic stem cell transplantation

BY DR. KARINE KLEINHAUS OF PLURISTEM THERAPEUTICS

EMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) is a broad term that covers the transplantation of blood progenitor/stem cells from any source. It has become a powerful tool to treat numerous conditions. Indeed, physicians perform more than 50,000 first HSCTs annually; of these, 53 percent are autologous (taken from the patient) and 47 percent are allogenic (taken from a donor other than the patient).

Among the conditions HSCT can treat are: acute myeloid leukemia, acute lymphoblastic leukemia, chronic myeloid leukemia, chronic lymphocytic leukemia, myelodysplastic syndromes, multiple myeloma, non-Hodgkin lymphoma, Hodgkin disease, aplastic anemia and pure red-cell aplasia—but this list is far from exhaustive.

HSCT has four possible outcomes: failure (when the transplanted cells just don’t take, a rare result); partial success (commonly called incomplete engraftment, when the cells are living inside the patient’s bone, but they are not active enough to keep the patient transfusion-independent); success with complications (when the cells are active enough to make the patient transfusion-independent but other health issues arise); and success without complications. In the first case, a second transplant is possible or other therapies can be considered, but the prognosis is usually disheartening.

Incomplete engraftment

Incomplete engraftment (poor graft function) requires the patient to undergo more transfusions of red cells or platelets. There are complications of serial transfusions of either of these cell types, and a patient needs intensive prophylactic treatments to protect from infections if his or her white counts are low. The current treatment for incomplete hematopoietic recovery includes administration of factors stimulating white and red blood cell growth, such as granulocyte-colony stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF) and erythropoietin.

However, a significant number of patients do not respond to growth factors and may continue to require frequent transfusions, which expose them to transfusion-related risks such as allo sensitization and infections, without providing a definitive cure. Regular transfusions are also associated with significant costs. Thus, there is an unmet need for additional treatment options for these patients.

Several groups are conducting trials to determine whether cellular therapy could be the treatment of choice for poor graft function after HSCT. Pluristem Therapeutics, based in Haifa, Israel, is currently recruiting patients in the United States and Israel for its Phase 1 trial of PLX-R18 cells, derived from mesenchymal-like cells collected from donated placenta, are designed to release a combination of therapeutic proteins to jump-start the regeneration of a poorly functioning hematopoietic system. The cells are also being evaluated in a variety of other hematologic indications.

Other groups are also working on cell therapies for the treatment of poor graft function after HSCT. These include a group of researchers from multiple academic institutions in Belgium, headed by Yves Beguin from the University Hospital of Liège. Their ongoing Phase 2 study is evaluating whether infusion of mesenchymal stem cells (MSCs) can treat steroid-resistant acute graft-versus-host disease (GVHD) or poor graft function after HSCT. The study is expected to be completed in December 2019. Researchers from several academic institutions in China—headed by Qifa Liu, of the Nanfang Hospital of Southern Medical University—are also studying MSCs as a therapy for poor graft function. One trial is testing whether MSCs with or without peripheral blood stem cells could treat poor graft function and delayed platelet engraftment. In another trial, this group is evaluating whether peripheral blood stem cells combined with MSCs can treat poor graft function.

Side effects of HSCT

Even when successful, HSCT can have some potentially dangerous side effects. Infections are quite common, though antibiotic treatments are usually successful. Organ damage and, among female patients, infertility are more difficult to address but can be managed in some cases. GVHD, which is common among allogeneic HSCT and rare in autologous HSCT, can be acute or chronic. This complication can be lethal and is often very difficult to treat.

GVHD

GVHD develops when the donor’s immune cells mistakenly attack the patient’s normal cells. GVHD can be mild, moderate or severe—even life-threatening. An ounce of prevention is always worth a pound of cure, so patients usually receive a regimen of preventative immune suppressors a day or two before their infusion. The regimen may include: Cyclosporine and methotrexate, Tacrolimus (Prograf) and mycophenolate mofetil (CellCept) as well as Prograf and sirolimus (Rapamune).

However, GVHD still happens, and it comes in two varieties, acute and chronic. Acute GVHD usually manifests within 100 days following HSCT. It is induced by donor T cells responding to the mismatched host polymorphic histocompatibility antigens. Chronic GVHD generally manifests later (>100 days) and has some features of other autoimmune diseases. It may develop either de novo or following resolution of—or as an extension of—acute GVHD.

Acute GVHD

Treatment of acGVHD can take many forms. Topical corticosteroids (e.g., triamcinolone 0.1%) have proven effective for some skin acGVHD. Often, physicians will continue the immunosuppressive prophylaxis associated with GVHD (e.g., calcineurin inhibitors or FK-506) while adding methylprednisolone.

Additional therapies, which can be used include mycophenolate mofetil, specific immunotoxin, anti-interleukin-2 (IL-2) receptor, ATG, mycophenolate mofetil, sirolimus and Xoma-Zyme (a pan T-Cell receptor immunotoxin). There is no data from a well-conducted controlled trial showing that any of these is more effective than any other.

If these initial therapies fail, secondary therapies include ATG or multiple pulses of methylprednisolone, Sirolimus, Infliximab, Enatacept, Mycophenolate mofetil (MMF) and Ruxolitinib, among others.

In August 2017, the FDA expanded the approval of Imbruvica (ibrutinib) for the treatment of adult patients with chronic GVHD (cGVHD) after failure of one or more treatments. This is the first FDA approved therapy for the treatment of cGVHD. Dr. Richard Pazdur, director of the FDAs Oncology Center of Excellence and acting director of the Office of Hematology and Oncology Products, said: “We are excited about the potential of Imbruvica for patients with cGVHD who do not respond to other forms of therapy—typically corticosteroids to suppress the immune system—now have a treatment option specifically indicated to treat their condition.” Imbruvica, a kinase inhibitor, was previously approved for treating certain chronic lymphocytic leukemias, Waldenstrom’s macroglobulinemia and marginal zone lymphoma. It is under accelerated approval status for mantle cell lymphoma. However, some cGVHD is steroid refractory. Currently, there are no approved therapies for patients with steroid refractory cGVHD in the United States, and off-label options have demonstrated mixed efficacy. These therapies include agents such as mycophenolate mofetil (MMF), etanercept, photopheresis, mesenchymal stromal cells, sirolimus and pentostatin. Other agents that can be tried include monoclonal antibodies directed against such targets as CD25, TNF-alpha, the T cell receptor, and the IL-2 receptor. There are limited data to guide the choice of therapy. Mesoblast is developing MSC-100-IV to treat these cases, and it has demonstrated preclinical properties to regulate T cell-mediated inflammatory responses by inhibiting T cell proliferation and down-regulating the production of the pro-inflammatory cytokines, including tumor necrosis factor-alpha, or TNF-alpha, and interferon gamma.

Chronic GVHD

Although the clinical presentation of cGVHD mostly resembles scleroderma, it can mimic many other autoimmune diseases. Immune suppression with corticosteroids, tacrolimus and mycophenolate mofetil are the mainstay of treatment. Hydroxychloroquine, an antimalarial drug, is effective in several autoimmune disorders, including cGVHD. A major cause of death in cGVHD is infection from profound immunodeficiency associated with the disease. All patients require prophylaxis against encapsulated organisms, and patients with frequent infections and low immunoglobulin levels should receive intravenous immunoglobulin replacement.

Mary E.D. Flowers and Paul J. Martin noted in Blood, “Management of chronic GVHD has relied on corticosteroids as the mainstay of treatment of ≥3 decades …. Pro-longed systemic corticosteroid treatment causes significant toxicity, including weight gain, bone loss, myopathy, diabetes, hypertension, mood swings, cataract formation and increased risk of infection.”

“Several groups are conducting trials to determine whether cellular therapy could be the treatment of choice for poor graft function after HSCT.”

 Approximately 50 to 60 percent of cGVHD patients who undergo systemic treatment require a secondary treatment within two years of their initial treatment. “No consensus has been reached regarding the optimal choice of agents for secondary treatment of chronic GVHD, and the published literature provides little useful guidance.” Physicians generally use 2 or 3 regimens of corticosteroids, cyclosporine and methotrexate, Tacrolimus and sirolimus, etanercept, infliximab, anti-TNF antibodies, anti-CD25 monoclonal antibodies, the mTOR inhibitor, or anti-CD52 monoclonal antibodies. As with the acute variety, some cGVHD is steroid refractory. Research into treatments again includes Pluristem’s PLX-PAD cell therapy. Last November, the company signed an agreement with Tel Aviv Sourasky Medical Center (Ichilov Hospital) to conduct a Phase 1/2 trial.

Conclusion

HSCT represents a revolution in the treatment of many maladies, but it is an incomplete revolution at present. Treatments of incomplete engraftment as well as acute and chronic GVHD are advancing but our understanding of the cases is far from complete. Studies to improve treatment are underway. However, our ability to prevent or quickly and easily remedy these health issues remains over the horizon. «

Karine Kleinhaus, M.D., M.P.H., is divisional vice president, North America at Pluristem Therapeutics.
Bacterial DNA uptake has IU scientists hooked

The first direct observation of the DNA uptake process could help advance efforts against drug-resistant bacteria

BY MEL J. YEATES

I.Indiana University scientists have made the first direct observation of a key step in the process that bacteria use to rapidly evolve new traits, including antibiotic resistance.

Using methods invented at IU, researchers recorded the first images of bacterial appendages—over 10,000 times thinner than human hair—as they stretched out to catch DNA. These DNA fragments can then be incorporated into bacteria’s own genome through a process called DNA uptake, or horizontal gene transfer. The work was reported on June 11 in the journal Nature Microbiology.

“Horizontal gene transfer is an important way that antibiotic resistance moves between bacterial species, but the process has never been observed before, since the structures involved are so incredibly small,” said senior author Ankur Dalal, an assistant professor in the IU Bloomington College of Arts and Sciences’ Department of Biology. “It’s important to understand this process, since the more we understand about how bacteria share DNA, the better our chances are of thwarting it.”

The bacterium used in the study was Vibrio cholerae, the microbe that causes cholera. The bacterial structures used to catch DNA in the environment are extremely thin, hair-like appendages called pili.

“We chose to study Vibrio cholerae because it undergoes natural transformation readily in the environment. We also know a lot about the regulation of how Vibrio cholerae turns on the genes required for natural transformation, and so we can use that as a tool to make them take up DNA from the environment more often. It is also a very easy organism to work with and grows quickly, which makes it a great tool for studying basic biological questions,” according to Dalal and IU Ph.D. candidate Dalia Amulic.

Meanwhile, 64 percent of respondents cited economic sustainability as a major or moderate biobank challenge, the second highest of 13 choices.

Fourty-two biobanks answered an iSpecimen online questionnaire about their work in March, and 67 percent of the participating biobanks cited underutilization of samples as a major or moderate biobank challenge—the most frequently cited of 13 choices. More than half (53 percent) of the participants said they collect more samples in storage, and that biobanks want to do something about it. Broader sample sharing would address both the underutilization and specimen availability problems, as well as the challenge of economic sustainability.

“As iSpecimen notes, one National Cancer Institute study found that four out of five researchers reported limiting the scope of their work due to the difficulty of procuring high-quality specimens,” according to Dalia and IU Ph.D. candidate Dalia Amulic.
Although scientists were aware that pili play a role in DNA uptake, direct evidence demonstrating how they work was lacking until this study. In order to observe pili in action, the scientists used a new method invented at IU to “paint” both the pili and DNA fragments with special glowing dyes. The team that developed this new method to label pili with dyes was led by IU Distinguished Professor Yves Brun and Ellison.

Dalia and Ellison explained that, “in order to record cells binding onto DNA using their pili, we first had to fluorescently label both the pili and DNA. While labeling DNA is very straightforward and can be easily achieved using commercially available dyes, we had to develop a method to label the pili because these tools did not exist. To label the pili, we genetically engineered them so that we could add a fluorescent dye that would bind to this modification. The kinds of dyes used to label the pili are called maleimide dyes. These dyes work by specifically binding to the thiol group of the amino acid cysteine, which we genetically engineered into the pili.

This method for labeling pili was developed by the first author of this study, Courtney Ellison, in Yves Brun’s lab, and it was initially published last year in collaboration with Ankur Dalia in the journal Science.

The new study uses these dyes to reveal that pili act like microscopic “harpooners” that cast their line through pores in the cell’s wall to “spear” a stray piece of DNA at the very tip. The pili then “reel” the DNA into the bacterial cell through the same pore. Dalia said the pore is so small that the DNA would need to fold in half to fit through the opening in the cell.

“It’s like threading a needle,” said Ellison. “The size of the hole in the outer membrane is almost the exact width of a DNA helix bent in half, which is likely what is coming across. If there weren’t a pilus to guide it, the chance the DNA would hit the pore at just the right angle to pass into the cell is basically zero.”

“We like to think of the pili as bacterial fishing rods,” Dalia and Ellison tell DDNews. “The pili are extended (or ‘cast’) and retracted (or ‘reeled’) back into the cell through tiny machines inside of the cell. The pili have specific proteins on their tips called minor pilins that they use as ‘fishing hooks’ to bind onto DNA, and when the pili are reeled back in they bring the attached DNA back with them.”

“One really exciting aspect of this research is that we found that the machinery used to retract or ‘reel’ the pili in the pili is not actually required for this to occur. This was very surprising, since it was always thought before that this machinery was needed for retraction to happen,” they note. “This is another future direction that we are pursuing by trying to determine how the cells are able to reel in their pili when that machine is missing.”

According to Ellison and Dalia, “One area directly related to this work will be to try to understand how the protein associated with the tip of the fiber latches onto DNA and what interactions are occurring between those proteins and the DNA. We are very interested in the role and range of forces required for bending DNA to pull it into the cell, and we hope to learn more about these factors in the future by studying the machines that extend and retract the pili.

“Also, type IV pili can carry out very diverse processes, including attachment to surfaces, virulence and horizontal gene transfer. The pilus labeling method used here is allowing us to pursue many unanswered questions about these structures, so another major area of focus moving forward is to apply this method to study other pilus systems in Vibrio cholerae and beyond.”

“These are really versatile appendages,” Dalia said. “This method invented at IU is really opening up our basic understanding about a whole range of bacterial functions.”
The scientists developed and tested a set of two factor codes to determine which ones were capable of programming skin cells to become neurons instead, particularly ones that recreate neuronal shape and electrical excitability. They tested 598 pairs of transcription factors altogether, and found that more than 12 percent were capable of producing neurons. This provides researchers with 75 new codes for the production of neurons.

Equally encouraging was the behavior of what Dr. Kristin Baldwin, a professor at Scripps Research and senior author of the study, referred to as the “synthetic neurons”—the converted neurons began to grow synapses and attempt to communicate with each other in the span of just a couple weeks.

To determine whether the new codes would produce different variations of neurons, Sohyon Lee, a co-first author on this research and recent Ph.D. graduate at Scripps Research, and Dr. Rachel Tsunemoto, also co-first author, turned to the “outputs” of the codes they’d worked with using electrical recording methods as well as new sensitive sequencing methods. Tsunemoto was a researcher with Scripps Research and the University of California, San Diego, at the time of the study.

They discovered that each code did indeed result in neurons with different properties. As the authors reported in their abstract, “By comparing the transcriptomes of these induced neuronal cells (iN cells) with those of endogenous neurons, we define a ‘core’ cell-autonomous neuronal signature. The iN cells also exhibit diversity; each transcription factor pair produces iN cells with unique transcriptional patterns that can predict their pharmacological responses. By linking distinct transcription factor input ‘codes’ to defined transcriptional outputs, this study delineates cell-autonomous features of neuronal identity and diversity and expands the reprogramming toolbox to facilitate engineering of induced neurons with desired patterns of gene expression and related functional properties.”

Baldwin called the results “a big step forward in cellular reprogramming,” as the use of the transcription factor “codes” means scientists can generate the exact types of neurons they want ad nauseam. This is particularly momentous when it comes to neurons, since, as noted online by Baldwin’s lab, “[N]eurons are primarily generated at birth and are maintained without cell division for the life of an individual. Neurons do not divide and have not been shown to generate tumors, for unknown reasons. The inability to generate cell lines from neurons precludes a number of important studies including analyses of neuronal genomic stability in differentiation and disease, and has impeded the generation of appropriate in-vitro models of disease.”

According to Baldwin, this research comes on the heels of years of work by her lab and others around the world. Nobel laureate Shinya Yamanaka and Marius Wernig’s group at Stanford University demonstrated that using sets of three to four factors enabled the conversion of skin cells into pluripotent stem cells and straight into neurons, and Baldwin’s lab had proved that applying sets of two factors enabled them to produce specific neurons that respond to stimuli such as itchiness or pain. That work, published in Nature Neuroscience in November 2014, described how Baldwin’s lab converted skin cells into the neurons responsible for registering sensation. These neurons are normally found in clusters known as dorsal root ganglia along the outer spine, and are affected by spinal cord injury and linked with Friedrich’s ataxia. Recent research has also tied them to aging and autoimmune disease.

“The brain is incredibly complex, with thousands of different types of cells that are each involved in different diseases,” says Baldwin, who was senior author of the study. “The problem with understanding and treating the many disorders of the brain is that we cannot reproducibly produce the right types of brain cells. Now we have found more than 75 new ways to rapidly and reproducibly turn skin cells into neurons that we think will be much better representatives of different neurologic diseases than were previously available.”

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Research & Development

Veterinary drug could curb malaria and Zika outbreaks

Calibr researchers look at a class of drugs called isoxazolines with an eye toward human use

BY DONNEWS STAFF

LA JOLLA, Calif. — Medicines given to household pets to kill fleas and ticks might be effective for preventing outbreaks of malaria, Zika virus infection and other dangerous insect-borne diseases that afflict millions of people worldwide, according to a new study led by scientists at Calibr, a non-profit drug discovery institute closely affiliated with Scripps Research, and TropiQ Health Sciences, a Dutch social enterprise.

The researchers found that a class of drugs called isoxazolines, sold in veterinary products such as Bravecto (bevecnaz) and axofluraner (NexGard) to protect pets from fleas and ticks, also kill species of disease-carrying mosquitoes that feed on human blood.

The research team, led by TropiQ’s Dr. Koen Dechering and Calibr’s Dr. Matt Tremblay, determined via experimental studies on mosquitoes and computer modeling that giving isoxazoline drugs to less than a third of the population in areas prone to seasonal outbreaks of insect-borne diseases could prevent up to 97 percent of all cases of infection. The results of the study were published recently in the Proceedings of the National Academy of Sciences (PNAS).

“Insect-borne infectious diseases remain primary causes of severe illnesses and fatalities worldwide, and new approaches to preventing outbreaks of these diseases are critically needed,” said Dr. Peter Schultz, CEO of Calibr and Scripps Research. “Our findings suggest that isoxazolines might be effective at controlling outbreaks of diseases carried by mosquitoes and other insects in regions with limited medical infrastructure.”

Millions of people each year contract malaria, Zika fever and other insect-borne diseases that are particularly prevalent in tropical and sub-tropical regions. In 2016, an estimated 216 million people contracted malaria worldwide and 445,000 died from the disease (mostly children in the African Region), according to the U.S. Centers for Disease Control and Prevention. Zika, a mosquito-borne disease that can cause birth defects in infants born to infected mothers, has spread rapidly around the planet in recent years and is now found in 90 countries.

“Research on insect-borne diseases has predominantly focused on control of insect populations through use of insecticides and prevention of bites through distribution of bednets, but these approaches have not been fully effective in controlling outbreaks,” says Koen Dechering, CEO of TropiQ Health Sciences. “Vaccines are largely lacking for most diseases and drugs to treat people who have contracted the disease are losing efficacy because of emerging resistance.”

The international research team investigated a new strategy, the possibility of giving human isoxazolines to block transmission of diseases by insect vectors.

When administered orally, the drugs are absorbed into the bloodstream and spread throughout the animal’s body, where they remain active for up to three months. While well tolerated in dogs and cats, the drugs kill blood-sucking fleas and ticks that feed on the blood of treated animals by damaging the insects’ nervous systems.

The Calibr and TropiQ scientists and their collaborators tested two of the drugs, Bravecto and axofluraner, and found they also kill species of disease-carrying mosquitoes and sand flies that feed on human blood infused with the insecticides. The drugs also were effective against insect strains that are resistant to common insecticides.

Based on existing data from studies of the drugs in animals, the researchers estimated that a single human dose of the drugs would convey an insecticidal effect against mosquitoes and sand flies lasting 50 to 90 days.

“In many regions where seasonal outbreaks are endemic, medical infrastructure is such that delivery of medical care is on an intermittent basis,” said Tremblay, chief operating officer of Calibr and Scripps Research and a senior author on the PNAS paper. “Isoxazolines could be administered prior to the beginning of seasonal disease outbreaks to convey protection until the threat diminishes at the end of the season.”

The drugs may not work as vaccines, since a treated person could still contract a disease from an insect bite. But an insect that bites an infected person taking the drugs would die before it could transmit the disease to other people, an effect that, when multiplied over a large population, would reduce the overall number of infections.

Based on safety studies of isoxazoline use in animals, the drugs have a good chance of being safe if repurposed for human use, according to Calibr. The research team is planning to evaluate the efficacy of the drugs in humans, and anticipates that these studies will take around two years.

Dr. Borko Amulic will use a £1.2-million, five-year award to study the natural ability of neutrophil immune cells (pictured here) to fight infection and perhaps boost them for therapeutic uses “in the post-antibiotic age.”

This shows a female Aedes aegypti, a species of mosquito that carries the Zika virus. Researchers at Calibr, a non-profit drug discovery institute closely affiliated with Scripps Research, and TropiQ Health Sciences found that drugs given to pets to kill fleas and ticks might be effective at stopping transmission of insect-borne diseases such as Zika fever and malaria in humans.

Dr. Borko Amulic explained that NETosis is an anti-microbial effector. These anti-microbial effectors include, as expected, the anti-microbial proteins of the neutrophil granules. Perhaps unexpectedly, the histones in NETs are also key components of the anti-microbial repertoire. It has long been known that histones are some of the most powerful anti-microbial agents that exist.

“Nevertheless, exactly how this anti-microbial activity of histones could be effectively harnessed was a long-standing and intractable mystery. The discovery of NETs presents a satisfying explanation for this apparent dilemma. Through NET formation, neutrophils provide histones with an opportunity to execute their alternative, non-structural function: microbial killing.”

Amulic and his team “want to understand how neutrophils are regulated at the molecular level and to use these insights to interrogate their function in immunity and inflammation,” he said. The researchers “also aim to develop therapies targeting neutrophils in malaria, a devastating disease that affects millions of people in developing countries.”

In Bristol, Amulic will work with key collaborators in the Faculty of Biomedical Science, including experts in the fields of immunology, microbiology and biochemistry. He will also have access to cutting-edge facilities such as the Wolfson Biomaging facility. With research that spans cell biology and immunology, the team will use molecular biology techniques such as CRISPR/Cas9 knockout to characterize genes regulating human neutrophil behavior. The researchers will employ various disease models and patient samples to investigate neutrophils in vivo.

As Amulic said, “Our goal is to propose targets for therapies in inflammatory diseases (including malaria, autoimmunity and cancer), as well as to discover ways to boost neutrophil microbial activity in settings such as immunodeficiency and antimicrobial resistance. The emergence of antimicrobial resistance threatens human health, and one strategy to combat infection is to boost the natural ability of neutrophils to kill pathogens. It is my hope that this award will allow us to discover the genes and biochemical pathways regulating neutrophil functions so we can do just that.”

He added, “I am also very keen to understand how neutrophils contribute to inflammatory diseases. Excessive neutrophil activation often damages our own tissues and contributes to diseases such as autoimmunity and cancer. By better understanding the link, we can begin to investigate how to negate this impact.”

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JULY 2018 || DDNEWS 15

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In the recurring debate of tau vs. amyloid, we take a look at how anti-tau research is progressing

BY JEFFREY BOYLEY

In looking at neurodegenerative diseases for this special focus section on neuroscience, it seemed fitting to check in not just on the consistently hot topic of Alzheimer’s disease, but more specifically the issue of the tau protein and some of the recent insights and progress on the anti-tau front.

Alzheimer’s has already proven to be a particularly complex and challenging disease for life-sciences researchers and pharma/biotech companies. And in a disease where sticky tangles of proteins seem to atrophy the brain and choke off cognition, one of the stickiest areas has been the issue of the amyloid protein vs. the tau protein. The aggregation of the tau protein is a hallmark of Alzheimer’s disease, but traditionally much of the energy and effort has gone toward focusing on ways to reduce the number of amyloid plaques.

As Emily Underwood wrote in a 2016 article in Science, “One of the telltale signs of Alzheimer’s disease (AD) is sticky plaques of β-amyloid protein, which form around neurons and are thought by a large number of scientists to bog down information processing and kill cells. For more than a decade, however, other researchers have fingered a second protein called tau, found inside brain cells, as a possible culprit.”

The topic Underwood was addressing was an imaging study of 10 people with mild AD that indicated tau deposits, rather than amyloid, are closely linked to memory loss, dementia and other AD symptoms. It wasn’t evidence that actually resolved the amyloid-tau debate—almost certainly both proteins play major roles, and perhaps other factors as well—but the findings did serve as a potential jumping-off point for additional effort on tau-targeting treatments and better diagnostic tools.

And on the subject that tau and amyloid likely represent more of a “pair of culprits” rather than an “either-or” situation, we can go back a couple years to a JAMA Neurology paper by G.S. Bloom that cast β-amyloid protein and tau in a “trigger and bullet” metaphor. As the author noted in the abstract, “During the past dozen years, a steadily accumulating body of evidence has indicated that soluble forms of Aβ and tau work together, independently of their accumulation into plaques and tangles, to drive healthy neurons into the diseased state and that hallmark toxic properties of Aβ require tau. For instance, acute neuron death, delayed neuron death following ectopic cell cycle reentry, and synaptic dysfunction are triggered by soluble, extracellular Aβ species and depend on soluble, cytotoxic tau. Therefore, Aβ is upstream of tau in AD pathogenesis and triggers the conversion of tau from a normal to a toxic state, but there is also evidence that toxic tau enhances Aβ toxicity via a feedback loop.”

Druggability of tau

So, fast forwarding back to the present day—or June 28, 2018, at least—we see one company continuing the trend toward more focus on tau as news came out of Cantabio Pharmaceuticals Inc. that the company, which is working on therapeutics for AD, Parkinson’s disease and related neurological disorders, had seen publication of a peer-reviewed article. Lead authored by Cantabio’s CEO Dr. Gergely Toth, along with collaborators at the Hungarian Academy of Sciences and German Center for Neurodegenerative Diseases (DZNE), the work appeared in the journal ACS Chemical Neuroscience.

The paper was titled “The structural basis of small molecule targetability of monomeric Tau protein” and reported structure-based evidence that native monomeric tau can be a viable target for drug-like small molecules despite its heterogeneous structure.

As the company noted in the news, the aggregation of monomeric tau protein is linked to the onset and progression of Alzheimer’s disease and other tauopathies, and this study and the scientific team’s previous findings provide theoretical and experimental evidence for the ability of monomeric tau to be a receptor of small molecules designed to prevent the aggregation, which leads to toxicity and cell death.

As per Prof. Eckhard Mandelkow, a co-author of the publication and group leader at DZNE in Bonn, this is further evidence that inhibition of tau aggregation by small molecules may be a viable therapeutic approach for tauopathies such as Alzheimer’s disease. He noted that “These molecules are currently being evaluated in animal models of tau-induced pathology. “We are excited to publish further scientific evidence that establishes a structural biology basis for Cantabio’s tau small-molecule pharmacological chaperone program, which aims to prevent and reduce aggregation of tau protein as a therapeutic strategy for Alzheimer’s disease and other tauopathies such as concussion-related chronic traumatic encephalopathy,” said Cantabio’s CEO, Dr. Gergely Toth. “The tau protein has long been a major target for Alzheimer’s drug development, but due to the nature of its structure, it has historically proven to be a difficult target for small-molecule drug candidates. Our work at Cantabio represents a significant step forward in developing a therapy that is able to prevent the formation of the toxic protein aggregates that are associated with neurodegeneration in these diseases.”

Tau as a therapeutic and diagnostic target

And, perhaps in a sign of how much tau research remains in the shadow of amyloid research, our next piece of fairly recent news comes from...
the end of last year, when AC Immune SA, a clinical-stage biopharmaceutical company with a broad pipeline focused on neurodegenerative diseases, shared the top-level insights from a key opinion leader (KOL) luncheon meeting on the importance of tau as a target in Alzheimer's disease and other neurodegenerative diseases. The meeting featured presentations by KOLs Dr. Khalid Iqbal of the New York State Institute for Basic Research in Developmental Disabilities and Dr. Michael Rafii of the University of California, San Diego, and the University of Southern California.

Iqbal highlighted the critical importance of tau as a therapeutic target in Alzheimer's disease and other neurodegenerative diseases and how inhibition and prevention of the Tau pathology can potentially rescue the pathology of Alzheimer's disease and cognitive impairment, commenting: “Neurodegeneration leads to tau pathology, and tau pathology leads to neurodegeneration. Where there is no tau pathology, there is no Alzheimer's disease. Tau-based therapeutic approaches have significant potential to treat a range of neurodegenerative diseases.”

“We are excited to publish further scientific evidence that establishes a structural biology basis for Cantabio’s tau small-molecule pharmacological chaperone program, which aims to prevent and reduce aggregation of tau protein as a therapeutic strategy for Alzheimer’s disease and other tauopathies such as concussion related chronic traumatic encephalopathy.”

Dr. Gergely Toth, CEO of Cantabio Pharmaceuticals

Rafii discussed tau-mediated pathology and the importance of tau diagnostics in people with Down syndrome, a population with a genetic predisposition to develop Alzheimer’s-related neuropathological changes, including ß-amyloid plaques and tau tangles.

“Biomarkers of Alzheimer’s, including Tau-PET, can be readily studied in adults with Down syndrome as in other preclinical AD populations,” Rafii noted. “By understanding the link between Alzheimer’s and Down syndrome, we may not only be able to help the Down syndrome community, but the broader population as well. People with Down syndrome are an important population to study as we enhance our understanding of early intervention and prevention of Alzheimer's disease in general.”

Also at the KOL meeting, Dr. Andreas Muh, chief scientific officer of AC Immune, highlighted the company’s relevant Tau programs:

- ACI-35, an anti-tau vaccine in Phase 1b and developed in collaboration with Janssen Pharmaceuticals under a 2014 licensing agreement
- ACI-70, an anti-tau antibody in Phase 2 and developed in collaboration with Genentech under a 2012 licensing agreement
- Morphomer Tau, a small molecule in preclinical development and developed in-house
- PI-2620, a Tau-PET imaging agent developed in collaboration with Piramal Imaging under a 2014 licensing agreement.

“We are delighted to share the valuable insights of these world-leading experts with our investors and stakeholders. These types of exchanges are vital so we can all work more together.”
CONTINUED FROM PAGE 17

Also late in 2017, TauRx Therapeutics Ltd. reported the full results from its second Phase 3 clinical study of LMTX, a tau aggregation inhibitor for Alzheimer’s disease, which were published online in the Journal of Alzheimer’s Disease. The company noted that results from this study (TRx-237-005) are consistent with those from the first Phase 3 study, recently published in The Lancet in mild to moderate Alzheimer’s disease, in supporting the hypothesis that LMTX might be effective as monotherapy at a dose as low as 4 mg twice daily.

The results of the earlier study showed significant differences in favor of two higher doses of LMTX (75 mg and 125 mg twice daily) when taken as monotherapy compared with the intended 4 mg control dose taken as monotherapy or as add-on therapy to currently approved treatments for AD in prespecified post-hoc analyses. In a further analysis, the same difference in favor of monotherapy compared with add-on treatment was found in patients taking the 4 mg twice-daily dose.

According to TauRx, in both the LMTX monotherapy and add-on therapy groups, whole brain atrophy (measured via MRI scans) initially progressed as expected for patients with mild Alzheimer’s disease. However, after nine months of treatment, the annualized rate of whole brain atrophy in monotherapy patients reduced significantly and became typical of that reported in normal elderly controls without Alzheimer’s disease. The comparable rate seen in the add-on therapy group progressed as reported for patients with mild Alzheimer’s disease.

And early this year, the company reported preclinical study results, “By understanding the link between Alzheimer’s and Down syndrome, we may not only be able to help the Down syndrome community, but the broader population as well. People with Down syndrome are an important population to study as we enhance our understanding of early intervention and prevention of Alzheimer’s disease in general.”

Dr. Michael Rafii of UC San Diego and USC published online in Frontiers in Molecular Neuroscience, showing that LMTM, the active pharmaceutical ingredient in the LMTX product developed for the treatment of Alzheimer’s disease, may also be useful for the treatment of Parkinson’s disease.

It is worth noting that in 2016, there was some significant disagreement regarding LMTM when Phase 3 results were presented showing that the drug missed its co-primary endpoints of slowing cognitive and functional decline in mild to moderate AD. Some had argued that the placebo and drug results were nearly identical and, as a commentator on the Alzforum website argued, a scientist involved in the trial presented “a subgroup analysis that held no statistical credence yet purported to show a strong benefit on cognition and brain atrophy.”

Some other takes around the same time contended that LMTM might not benefit AD patients who are receiving standard of care but, as a monotherapy, the drug might stabilize cognition and reduce brain atrophy.

Axovant licenses investigational gene therapy

BASEL, Switzerland—Axovant Sciences in early June announced that it had acquired the exclusive worldwide rights to develop and commercialize OXB-102, now AXO-Lenti-PD, from Oxford BioMedica. AXO-Lenti-PD is an investigational gene therapy for Parkinson’s disease that delivers a therapeutic genetic payload encoding a critical set of enzymes required for dopamine synthesis in the brain. Oxford BioMedica is a world leader in lentiviral vector product development and manufacturing, and will be the clinical and commercial supplier of AXO-Lenti-PD. Axovant expects to initiate a Phase 1/2 dose escalation study of AXO-Lenti-PD in patients with advanced PD by the end of 2018.

Under the terms of the license agreement with Oxford BioMedica, Axovant obtained rights to AXO-Lenti-PD, as well as its predecessor product ProSavin, for an initial payment of $50 million in cash, $5 million of which will be applied as a credit against the process development work and clinical supply that Oxford BioMedica will provide to Axovant. Oxford BioMedica is also eligible to receive additional development, regulatory and commercial milestone payments potentially in excess of $120 million, and tiered royalties on net sales of AXO-Lenti-PD, if approved. Rovaant has agreed to purchase $25 million of Axovant common shares, which will support the clinical development of AXO-Lenti-PD and additional business development activities.

Picking apart PD

A roundup of recent news on R&D related to Parkinson’s disease

BY JEFFREY BOULEY

NEW YORK—A recent study from researchers at the Icahn School of Medicine at Mount Sinai provides new insights into a link between inflammatory bowel disease (IBD) and Parkinson’s disease (PD), and may have significant implications for the treatment and prevention of PD.

The study, published in JAMA Neurology, shows that individuals with IBD are at a 28-percent higher risk of developing PD than those without IBD. However, if they are treated with anti-tumor necrosis factor alpha (anti-TNFα) therapy, a monoclonal antibody that is commonly used to control inflammation in IBD patients, then their risk of developing Parkinson’s goes down significantly and becomes even lower than that in the general population.

These new insights may allow for better screening of IBD patients for Parkinson’s disease, given that IBD onset usually precedes that of PD by decades, and they also offer evidence to support exploring anti-TNFα therapy to prevent PD in at-risk individuals.

While previous research had shown genetic and inflammatory connections between IBD and Parkinson’s disease, clinical evidence linking the two has been scarce. The authors of the study previously identified a number of genetic signals that contributed to either an increased risk of both PD and of Crohn’s disease, a type of IBD, or a decreased risk of both diseases, which prompted them to further study the co-occurrence of the two diseases.

“Systemic inflammation is a major component of IBD, and it’s also thought to contribute to the neuronal inflammation found in Parkinson’s disease,” explained Inga Peter, a professor in the Department of Genetics and Genomic Sciences at Mount Sinai and lead investigator in the study. “We wanted to determine if anti-TNFα therapy, could mitigate a patient’s risk in developing Parkinson’s disease.”

The Mount Sinai team found a 78-percent reduction in the incidence of Parkinson’s disease among IBD patients who were treated with anti-TNFα therapy when compared to those who were not.

It was previously thought that anti-TNFα therapies had limited effects on the central nervous system, the site where molecular mechanisms of PD are found, because the large molecules in the anti-TNFα compounds cannot independently pass through the blood-brain barrier. The outcomes of this study suggest that it may not be necessary for the drug to pass through the blood-brain barrier to treat or prevent inflammation within the central nervous system, or that the blood-brain barrier in patients with PD may be compromised, allowing the large molecules of the compound to pass through.

Preclinical evidence for DJ-1 protein targeting

SAN FRANCISCO—Cantabio Pharmaceuticals Inc. recently presented results of the company’s DJ-1 protein-targeting small-molecule pharmacological chaperone therapeutic program at the NeuroD Conference (Advances in Drug Discovery for Proteopathic Neurodegenerative Diseases) in Mainz, Germany.

Loss of DJ-1 protein function has been linked to the onset of a variety of diseases, such as Parkinson’s disease, Alzheimer’s disease, stroke, amyotrophic lateral sclerosis, chronic obstructive pulmonary disease and type 2 diabetes. The DJ-1 protein is considered to be one of the primary therapeutic targets for Parkinson’s disease, as it is genetically linked to the onset of familial PD.

The presentations described the positive therapeutic activity in cellular models and in an MPTP mouse model of PD of Cantabio’s novel DJ-1 candidates.

New data presented for Titramet (AXO-010) is the DJ-1 protein targeting small-molecule pharmacological chaperone that this drug candidate has shown drug-like characteristics and its significant protective function in a recognized mammalian disease model for Parkinson’s disease is a major step forward for Cantabio’s drug development programs,” said Cantabio’s CEO, Dr. Gergely Toth. “We are looking forward to testing this molecule in further disease models of Parkinson’s and Alzheimer’s disease and to the further development of multiple candidates from our other programs. These results also provide excellent validation of our in-house DJ-1 drug discovery platform’s ability to generate prospective drug candidates and for our DJ-1 targeting therapeutic program’s potential for becoming a disease-modifying therapeutic for Parkinson’s and Alzheimer’s disease.”
Neuroscientists discover roles of AD-linked gene

Study may reveal why people with the APOE4 gene have higher risk of the disease

BY ANNETTRAFTON, MIT NEWS OFFICE

CAMBRIDGE, Mass.—People with a gene variant called APOE4 have a higher risk of developing late-onset Alzheimer’s disease; in fact, APOE4 is three times more common among Alzheimer’s patients than it is among the general population. However, little is known about why this version of the APOE gene, which is normally involved in metabolism and transport of fatty molecules such as cholesterol, confers higher risk for Alzheimer’s.

To shed light on this question, MIT neuroscientists have performed a comprehensive study of APOE and the more common form of the gene, APOE3. Studying brain cells derived from a type of induced human stem cells, the tests revealed that APOE4 promotes the accumulation of the beta amyloid proteins that cause the characteristic plaques seen in the brains of Alzheimer’s patients.

“APoE4 influences every cell type that we studied, to facilitate the development of Alzheimer’s pathology, especially amyloid accumulation.”

Li-Huei Tsai, director of MIT’s Picower Institute for Learning and Memory

“APoE4 influences every cell type that we studied, to facilitate the development of Alzheimer’s pathology, especially amyloid accumulation,” says Li-Huei Tsai, director of MIT’s Picower Institute for Learning and Memory and the senior author of the study. The researchers also found that they could eliminate the signs of Alzheimer’s in brain cells with APOE4 by editing the gene to turn it into the APOE3 variant.

The researchers recently delved deeper to try to understand why that is the case. They genetically converted the APOE4 gene to APOE3 in brain cells derived from a healthy subject to APOE4. Because the cells were genetically identical except for the APOE gene, any differences seen between them could be attributed to that gene.

Previous studies have shown that people with the APOE4 gene have higher levels of amyloid proteins, but little is known about why that is. In this study, the MIT team set out to answer that question using human induced pluripotent stem cells—stem cells derived from skin or other cell types. They were able to stimulate those stem cells to differentiate into three different types of brain cells: neurons, astrocytes and microglia.

Using the gene-editing system CRISPR/Cas9, the researchers genetically converted APOE3 in stem cells derived from a healthy cell with APOE4 by editing the gene to turn it into the APOE3 variant.

The APOE4 variant of the APOE gene is known to be associated with Alzheimer’s disease, but MIT researchers recently delved deeper to try to understand why that is the case. They genetically converted the APOE4 gene to APOE3 in brain cells derived from a healthy subject to APOE4. Because the cells were genetically identical except for the APOE gene, any differences seen between them could be attributed to that gene.

In neurons, the researchers found that cells expressing APOE3 and APOE4 differed in the expression of hundreds of genes—about 250 genes went down and 150 went up in cells with APOE4. In astrocytes, the numbers were even higher, and they were highest of all in microglia: in APOE4 microglia, more than 3,100 genes showed reduced activity, while 300 became more active. These genetic changes also translated to differences in cell behavior. Neurons with APOE4 formed more synapses, and they secreted higher levels of amyloid protein.

In APOE4 astrocytes, the researchers found that cholesterol metabolism was highly dysregulated. The cells produced twice as much cholesterol as APOE3 astrocytes, and their ability to remove amyloid proteins from their surroundings was dramatically impaired. Microglia were similarly affected. These cells, whose normal function is to help remove foreign matter, including amyloid proteins and pathogens such as bacteria, became much slower at this task when they had the APOE4 gene.

The researchers also found that they could reverse most of these effects by using CRISPR/Cas9 to convert the APOE4 gene to APOE3 in brain cells derived from induced stem cells from a patient with late-onset Alzheimer’s disease.

Disrupting cell behavior

In another experiment, the researchers created three-dimensional “organoids,” or miniature brains, from cells with genes that are known to cause early-onset Alzheimer’s. These organoids had high levels of amyloid aggregates, but when they were exposed to APOE3 microglia, most of the aggregates were cleared away. In contrast, APOE4 microglia did not efficiently clear the aggregates.

Tsai said she believes that APOE4 may disrupt specific signaling pathways within brain cells, leading to the changes in behavior that the researchers saw in this study.

“From this gene expression profiling, we can narrow down to certain signaling pathways that are dysregulated by APOE4," she says. “I think that this definitely can reveal potential targets for therapeutic intervention.”

The findings also suggest that if gene-editing technology could be made to work in humans, which many biotechnology companies are now trying to achieve, it could offer a way to treat Alzheimer’s patients who carry the APOE4 gene.

“If you can convert the gene from E4 to E3, a lot of the Alzheimer’s-associated characteristics can be diminished,” Tsai says.
**CRV431 tackles liver fibrosis**

EIDSON, N.J.—ContraVir Pharmaceuticals Inc. has reported that a preclinical study of CRV431, a cyclophilin inhibitor, appeared to decrease the extent of fibrosis in an animal model by 48 percent compared to a control. Mice were treated with streptozotocin, then fed a high-fat diet. CRV431 was administered orally for eight weeks, during which time it had no effect on body weight, liver weight or blood glucose levels. Previous studies of the compound have shown it to have antiviral effects by reducing HBV DNA, surface antigen and other viral markers of HBV infections and/or liver disease.

“With these results, we have data indicating that CRV431 has an independent effect on reducing the formation of fibrosis that is over and above the effects on the hepatitis B virus,” James Sapirstein, CEO of ContraVir Pharmaceuticals, noted in a press release.

**New implants to improve data collection, animal welfare**

ST. PAUL, Minn. & HOLLISTON, Mass.—The second quarter of 2018 saw Data Sciences International, a subsidiary of Harvard Bioscience Inc., announce the launch of two telemetry implants: the PhysioTel Digital L03 and L04. The implants record data from conscious, unrestrained lab animals and can record any combination of up to four biopotential channels (such as EEG, EMG or ECG), temperature and activity in large animal models.

Jeffrey Duchemin, president and CEO of Harvard Bioscience, said, “DSI is committed to providing solutions for researchers that can improve the collection of high-quality physiologic signals and other metrics. Data Sciences International has been at the forefront of innovation in our industry.”

A collaboration between research groups from Indiana University and the Turku Centre for Biotechnology in Finland has collaborated in discovering an experimental molecule that appears to interrupt the signaling cascades in the body that cause multiple forms of neuropathic pain without producing unwanted side effects. The study was reported in the May 2018 issue of the journal Pain. The research was funded by the National Institutes of Health’s National Cancer Institute.

The researchers, who met at a Society for Neuroscience meeting, were led by Andrea Mandel, MPH, PhD, a scientist at Indiana University and the Turku Centre for Biotechnology in Finland, along with Andrea Mandel, MPH, PhD, a scientist at Indiana University and the Turku Centre for Biotechnology in Finland. The researchers reported that the molecule appears to interrupt signaling cascades in the body that cause multiple forms of neuropathic pain without producing unwanted side effects.

Hohmann of Indiana University and Michael Courtney from the Turku Centre for Biotechnology, Hohmann explained that the approach offers potential for maximizing the therapeutic efficacy of novel inhibitors likely to exhibit favorable analgesic profiles without negative side effects.
SIGNAL CONTINUED FROM PAGE 20

MANF CONTINUED FROM PAGE 20

while the inhibition of NF-B signaling pathway could be a potential mecha-

nism.” In other words, after a brain injury, heightened amounts of the MANF protein lessened the egregious effects of impact on the blood-brain-barrier (BBB), and thus lowered the risks of cerebral edema and inflammation.

Scientists found that in immediate aftermath of traumatic brain injury in rats, the body naturally flooded the brain with endogenous MANF. By adding a high dose of recombinant human MANF, the impact of TBI was dramatically reduced. Specifi-
cally, MRI’s conducted after the injury and following a high dose of exogenously produced MANF indicated a lower brain-water-content measurement. Likewise, the testing showed an increase in their modified Garcia score, which measures six indices of sensorimotor deficits, while also alleviating the blood-brain barrier permeability—a finding of particular interest to the scientists.

“The fact that MANF acts to restore the blood-brain barrier is highly consequen-
tial in terms of restoring one of the body’s crucial protective mechanisms. Further studies are required to understand how this mechanism would affect drug develop-
ment,” asserts Gerald Commissiong, CEO of MANF Therapeutics.

MANF was initially identified by parent company Amarantus’ own platform, the PhenoGuard protein discovery engine. In 2017, Amarantus formed MANF Therapeutics as a wholly owned subsidiary to continue preclinical development of MANF, initially for the treatment of ophthalmological disorders. Amarantus entered into a manufacturing agreement with Catal-
ent Pharma Solutions for clinical-grade production of MANF, with Catalent pro-
viding all cell line engineering, process development and clinical Good Manufac-
turing Practices (cGMP) biomanufacturing activities. Through that partnership, MANF Therapeutics had the tools for the rapid development of a high performance cell line expressing the MANF protein, thus enabling them to scale up for cGMP production.

The MANF protein has proven to be effective in managing other diseases attrib-
uted to inflammatory response, and had begun Investigational New Drug (IND)-
enabling development to utilize MANF for ophthalmological conditions, includ-
ing RAO and retinitis pigmentosa, back in 2016. It has already been granted orphan drug designations from the FDA for these conditions and has shown promise as a potential treatment for glaucoma, Parkin-
son’s, Alzheimer’s, diabetes and cardiovascular issues such as stroke and myocardial infarction. The results regarding its use in treating TBI, however, suggest a potential new indication, and has prompted the company to restart the IND preparations.

Amarantus has retained regulatory expertise to identify the fastest path to human proof-of-concept data by evaluating well-respected regulatory pathways available worldwide and is targeting the initiation of first-in-man clinical studies for MANF in 2019.

“These findings mean we will re-initiate cGMP manufacturing for MANF. This news is important because it speaks to MANF’s broad potential to protect brain cells from injury, and outlines key mechanisms into MANF’s biological function.”

Gerald Commissiong, CEO of MANF Therapeutics

The MANF protein was discovered by MANF Therapeutics’ chief scientific officer, Dr. John Commissiong, thanks to AMBS’ proprietary discovery engine PhenoGuard. MANF Therapeutics is developing MANF-based products as treatments for brain and ophthalmic disorders, and owns IP rights and licenses from a number of universities related to the development of the protein.

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APVO210 holds promise in the treatment of autoimmune diseases

**BY DDNEWS STAFF**

**SEATTLE—Aptevo Therapeutics Inc., a biotechnology company focused on developing novel oncology and hematologic therapeutics, recently announced the publication of preclinical data in Frontiers in Immunology. The data highlight the activity of APVO210 as a potent and selective immunosuppressive agent with potential utility in the treatment of multiple autoimmune and inflammatory conditions, such as psoriasis, inflammatory bowel disease, rheumatoid arthritis, graft-versus-host disease and lupus, as well as other diseases where there is antigen-driven activation of T lymphocyte-mediated disease. APVO210 is a hapten conjugate built on Aptevo’s ADAPTIR therapeutic technology platform. It is designed to modulate and suppress pathologic immune activation without antigen-presenting cell stimulation, allowing delivery of a modified form of IL-10 to antigen-presenting cells via CD86 without stimulating IL-10 responses on resting and activated lymphocytes. Cytokines are pleiotropic and function by promoting or suppressing a variety of cellular functions, including inflammatory responses. Unregulated inflammation is believed to be responsible for a variety of chronic and acute inflammatory and autoimmune disorders. The cytokine IL-10 is known to play a key role in suppressing inflammation and, as a result, has been studied extensively by other companies in different clinical trials for autoimmune and inflammatory disorders. Unfortunately, the results of these studies have been disappointing. This may be due to the undesired stimulatory properties of IL-10, which exerts stimulatory effects on lymphocytes, monocytes, and macrophages. In preclinical and immunogenic production and cytotoxic T-cell function, thus potentially reducing its overall therapeutic utility for immunosuppression.

Conversely, APVO210 is designed to deliver a modified form of IL-10 to suppress inflammation and immune activation without lymphocyte stimulation. Importantly, APVO210 also retains the ability to mediate the differentiation of tolerogenic dendritic cells and antigen-specific T regulatory cells (Tr1). "There is a growing body of data to support APVO210 as a novel, first-in-class targeted cytokine immunotherapy. "Our data highlight the unique attributes of this molecule, demonstrating its ability in vitro to selectively target antigen presenting cells without triggering IL-10R signaling in T or B cells,” Dr. Jane Gross, chief scientific officer for Aptevo, says. APVO210 demonstrates its unique and selective mechanism of action.

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This unique mechanism of action for delivering IL-10 in the treatment of autoimmune and inflammatory diseases where there is antigen-driven activation of T lymphocyte-mediated disease.

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New investment in treating superbugs

Melinta Therapeutics seeks to move investigational pyrrolocytosine compounds into clinical stage

BY RACHEL FLEHINGER

NEW HAVEN, Conn.—Backed by funding from CARB-X, Melinta Therapeutics is seeking a prime compound candidate to begin Investigational New Drug (IND) testing to treat drug-resistant bacterial infections. Development will continue on the company’s investigational pyrrolocytosine compounds, which are a novel class of antibiotics targeting bacterial ribosomes in entirely new ways.

“Our structure-based design efforts to create and optimize the pyrrolocytosine class of antibiotics have shown exciting promise, with several compounds demonstrating comprehensive activity and preclinical effect across the full set of bacterial ‘superbugs,’” said Dr. Erin Duffy, chief scientific officer at Melinta. “We believe this new class of antibiotics could be transformational in the fight against these urgent threats. The support and INVESTIGATIONAL Pyrrolocytosine compounds are a new class of antibiotics targeting bacterial ribosomes in entirely new ways. Our structure-based design efforts to create and optimize the pyrrolocytosine class of antibiotics have shown exciting promise, with several compounds demonstrating comprehensive activity and preclinical effect across the full set of bacterial ‘superbugs,’” said Dr. Erin Duffy, chief scientific officer at Melinta. “We believe this new class of antibiotics could be transformational in the fight against these urgent threats. The support and

THE NEW MIGRAINE MUFFLER(S)

Allergan’s oral CGRP receptor antagonist demonstrates robust efficacy and safety in episodic migraine prevention

BY MEL J. YEATES

DUBLIN—In early June, Allergan plc announced positive results from CDP-321, a Phase 2b/3 clinical trial evaluating the efficacy, safety and tolerability of orally administered atogepant. All active treatment arms of atogepant met the primary endpoint across all doses and dose regimens, with a statistically significant reduction from baseline in monthly migraine/probable migraine (MPM) headache days in patients with episodic migraine treated with atogepant compared with placebo for 12 weeks.

Atogepant is Allergan’s second orally-administered investigational calcitonin gene-related peptide (CGRP) receptor antagonist in development for migraine prevention. Atogepant follows ubrogepant, Allergan’s first oral investigational CGRP antagonist for the acute treatment of migraine, which reported two positive Phase 3 pivotal trial results earlier this year. Allergan will continue with its Phase 3 program for atogepant, following discussions with regulatory authorities.

“Our extremely pleased to share these positive results for atogepant—our first Phase 2b/3 study in episodic migraine—which

REVERSE-ing vision loss

GenSight’s GS010 improves vision in Phase 3 trial of patients with rare genetic disease

BY KELSEY KAUSTINEN

PARIS—Additional results shared in June from GenSight Biologics’ Phase 3 clinical trial, REVERSE, are building on previous encouraging data for its GS010 compound. REVERSE is a randomized, double-masked, sham-controlled pivotal Phase 3 trial evaluating the efficacy of a single intravitreal injection of GS010 (AAV2/2-ND4) in 37 Leber hereditary optic neuropathy (LHON) patients with the G11778A mutation in the mitochondrial ND4 gene.

“We are extremely pleased to share these positive results for atogepant—our first Phase 2b/3 study in episodic migraine—which

IN THIS SECTION

Infectious disease
Paratek highlights omadacycline efficacy .................................................. 23

Inflammatory disease
IMO-8400 falls short of primary endpoint ...................................................... 23

Migraine
The new migraine muffler(s) ................................................................. 23

Neurology
Cannabis vs. Lennox-Gastaut syndrome ....................................................... 24

REVERSE-ing vision loss .......................................................... 23

CLINICAL TRIALS
Melinta has not generally invested in resources available through CARB-X will provide important assistance as we move to advance antibiotics, “said Duffy. “We are very enthusiastic about our candidates progressing with CARB-X support, we are also being good stewards of the program and the company by also continuing to develop new products behind our existing candidates.”

Dr. Erin Duffy, chief scientific officer at Melinta

“With these findings, we demonstrate clearly that CBG is active at the cannabinoid receptors CB1 and CB2 and that it exerts its effects through those receptors. We have deepened the knowledge about phytocannabinoids and reopened the discussion about the interaction between the Cannabis plant compounds.”

Dr. Xavier Nadal of Phytoplanth Research

Cannabis vs. Lennox-Gastaut syndrome

Positive results published in NEJM for clinical trial of Epidiolex in LGS

BY DDNEWS STAFF

BOHEMIA, N.Y. — The New England Journal of Medicine (NEJM) recently published positive results from a clinical trial of cannabidiol in Lennox-Gastaut syndrome (LGS). Cannabidiol (CBD), a compound derived from the cannabis plant that does not produce a “high,” has been an increasing focus of medical research in epilepsy. New study results from the clinical trial of Epidiolex, the lead cannabidiol product candidate for GW Pharmaceuticals, indicate that the compound significantly reduced the number of seizures in patients with LGS.

Lennox-Gastaut syndrome is a rare and severe form of childhood-onset epilepsy that typically persists into adulthood. Despite currently available medications and a polytherapy approach to treatment, most individuals with LGS will continue to have seizures and associated comorbidities.

The results of the study published in NEJM compared two doses of CBD to placebo. Researchers reported a 41.9 percent reduction in "drop seizures" for those taking a 20 mg/kg CBD regimen and a 37.2 percent reduction in drop seizures in those on a 10 mg/kg regimen. Drop seizures are a type of seizure that results in a loss of muscle control and often leads to falls.

Researchers enrolled 225 patients ages 2 to 55 with LGS across 30 international sites in a randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of cannabidiol in patients. Side effects were reported in 94 percent of the patients in the 20 mg CBD group, 84 percent in the 10 mg group, and 72 percent of those taking the placebo. Side effects were generally reported as mild or moderate in severity and included sleepiness, decreased appetite, diarrhea, upper respiratory infections, fever, vomiting, nasopharyngitis and status epilepticus.

“This landmark study provides data and evidence that Epidiolex can be an effective and safe treatment for seizures seen in patients with Lennox-Gastaut Syndrome,” said Dr. Anup Patel, chair of the LGS Foundation’s professional advisory board, chief of neurology at Nationwide Children’s Hospital and the study’s co-first author says.

Added Christina SanMocenico, executive director of the LGS Foundation: “LGS is devastating. While it is rare to achieve complete seizure control in this patient population, we sincerely hope that more safe and effective treatment options become available so that patients and their families can have relief from unrelenting seizures.”

In other, unrelated news, a new study in cannabis extracts and journal publications, Phyto Plant Research S.L. participated in a first-ever pioneering collaborative project to investigate the ability of cannabinoid cannabigerol (CBG), the molecular precursor of Δ9-tetrahydrocannabinol (Δ9-THC) and cannabinoid (CBD). The study investigated the ability of the above to modulate the affinity and functionality of type-1 and type-2 cannabinoid receptors (CB₁ and CB₂, respectively) and CB₁-CB₂ hetero-receptor complexes. It concluded that CBG significantly modulates CB₁R and CB₂R-mediated endocannabinoid action, while the effects are weak in CB₁R-expressing cells.

The results of this research, published in the journal Frontiers in Pharmacology, suggest that CBG, a non-psychoactive phytocannabinoid, at nanomolar concentrations, is capable of acting as a competitive partial agonist of the CB₁R. Regarding its action on CB₁R, it is not possible to rule out a potential allosteric action, since the blocking of intracellular signaling of CB₁R in vitro occurs at concentrations of CBG lower than those necessary for its binding to the orthostatic site of the receptor.

These findings, the company says, “reopen the discussion” about the ability of other phytocannabinoids to bind directly to cannabinoid receptors as Δ9-THC does. In the study, researchers obtained results using different approaches that include the classic radioligand binding, new fluorescent-based binding techniques and the measurement of signaling pathways. In these assays, CBG was able to modify the affinity and activity of selective CB₁R and CB₂R agonists at concentrations with physiological relevance (nanomolar).

The results also suggest that the partial agonism on the CB₁R is regulated by the presence of the CB₁R. However, more complex alternative scenarios cannot be ruled out as CBG may act on the orthosteric site of the CB₁R protomer and as protein agonist of the CB₁R protomer within the CB₁R/CB₂R heteromer.

With these findings, we demonstrate clearly that CBG is active at the cannabinoi

"We have done a thorough job with our candidate compounds, ascertaining characterization and optimization activity, and we have very promising early safety results. But, of course, the proof is in the pudding", asserts Duffy. "While we are very enthusiastic about our candidates progressing with CARB-X support, we are also being good stewards of the program and the company by also continuing to develop new products behind our existing candidates in the event of an unexpected setback.”

The ribosome has been the focus of ongoing research into its structure and workings for decades, as a prime target for immunologists and drug discovery pipelines. Antibiotics have proven effective against disease by attacking bacteria, disrupting their ribosomes and thus preventing the bacteria’s ability to create proteins needed to survive and reproduce. However, bacteria have developed resistance to many antibiotics that have targeted the same ribosome sites via similar mechanisms. While an estimated 60 to 70 percent of antibiotics are effective against target-resistant bacteria, the discovery and development of new antibiotics has proven extremely challenging.

Melinta’s pyrrolocytosines have demonstrated comprehensive activity across the full set of bacterial “superbugs”.

“Melinta believes a key to ending superbugs is their focus on novel ways to target the bacterial ribosome in response to the alarming emergence of bacteria that have developed resistance to all existing drug classes. Melinta has demonstrated that CARB-X can fund a broader range of initiatives, is capable of acting as a competitive partial agonist of the CB₁R. Regarding its action on CB₁R, it is not possible to rule out a potential allosteric action, since the blocking of intracellular signaling of CB₁R in vitro occurs at concentrations of CBG lower than those necessary for its binding to the orthostatic site of the receptor.”

Dr. Xavier Nadal of Phyto Plant Research, not -
ganglion cells leads to irreversible vision loss. Vision is suddenly lost in one eye, and the second eye is sequentially impaired—while 97 percent of patients experience bilateral involvement at less than one year of the beginning of their vision loss, a quarter of patients lose vision in both eyes simultaneously. An estimated 1,400 to 1,500 individuals lose their sight as a result of LHON in the United States and Europe every year.

GS010 uses a mitochondrial targeting sequence proprietary technology platform that resulted from research performed at the Institut de la Vision. When linked with a gene of interest, the platform can specifically target defects in mitochondria using an AAV vector. The gene of interest is transported into the cell, where it is expressed and produces a functional protein, which is then moved to the mitochondria to restore missing/deficient mitochondrial function.

GenSight shared top-line results in April that demonstrated that the improvement of +11 ETDRS letters (-0.218 LogMAR on average) in GS010 treated eyes, which was clinically significant, was matched by an improvement of +10 ETDRS letters (-0.211 LogMAR) in the sham-treated eyes. This fell short of the study’s primary endpoint of a +15 ETDRS letters difference in visual acuity between GS010- and sham-treated eyes.

The study did meet its secondary endpoints based on spectral-domain optical coherence tomography (SD-OCT) parameters, such as the change in ganglion cell layer macular volume from baseline to week 48, and the change in thickness of the temporal quadrant of the retinal nerve fiber layer from baseline to week 48. In addition, contrast sensitivity—per Pelli-Robson low-vision testing, a more sensitive method of evaluating visual function—almost doubled in GS010-treated eyes compared to sham-treated eyes.

“-0.2 log units is about 11 to 12 letters,” Dr. Robert Sergott, professor of neurology and ophthalmology at Thomas Jefferson University, remarked in the webcast. “We set a high bar this trial—15 letters. If you get a 15-letter improvement, you double your visual angle, and regulatory agencies will allow you to label your product as one that gives vision improvement. The most common intravitreal injections are the anti-VEGF agents in the retinal community, for diabetes, macular degeneration of the wet variety. How much improvement do they get? Seven letters; this far exceeded [that].” Sergott is also the director of neuro-ophthalmology at Wills Eye Hospital and director of the William H. Amessley, Jr. EyeBrain Center.

The exact cause of the improvement in the sham-treated eyes is unknown, but it could be based in part on the fact that molecules can travel from one eye to the contralateral optic nerve, GenSight noted in its presentation. The company hypothesizes that GS010 is systemically absorbed, and as such, a smaller dose makes its way to the untreated eye.

As noted in the presentation, this is the first demonstration of neuro-protection of both central nervous system AXONS and neurons in a human genetic disease.

Examining the totality of the data, the REVERSE results suggest a therapy that may provide meaningful bilateral improvement of vision for our subjects, which is not what would be expected from the natural history of this disease. Our planned follow-up of REVERSE subjects will enable us to monitor the observed continuous bilateral improvement after another year,” said Dr. Barrett Katz, chief medical officer of GenSight. “GS010-treated eyes were significantly better when compared to sham-treated eyes. In addition, trends suggest a potentially larger benefit for subjects at earlier stages of LHON. We eagerly await what data from the RESCUE trial will show.”

Based on post-hoc analyses, it is thought that patients at less advanced stages of LHON could see a better benefit from GS010. Participants who enrolled with better vision had better clinical outcomes, and 75 percent of GS010-treated eyes that saw improvement at week 48 were those that had had vision loss for less than nine months at the time of treatment. Study subjects will be evaluated again at 96 weeks, with that data set to be available in the first quarter of 2019.

“The company—myself, and the management of this company—is absolutely determined to move this product into the approval process,” Bernard Gilly, co-founder and CEO of GenSight, said in the webcast, adding later: “We will move this forward to the European Agency, and to the FDA as well. We are going to make all effort possible to make this happen, to make this become a product available to the patient as soon as we can.”

For more information, visit www.DDN-News.com
Atogepant is an oral CGRP antagonist that provides pain relief from two to 24 hours, and the 50 mg dose demonstrated improvement, but failed to demonstrate statistical significance.

The 50 mg dose of ubrogepant also showed a statistically significant greater percentage of patients achieving pain relief at two hours, sustained pain relief from two to 24 hours, and sustained pain freedom from two to 24 hours after the initial dose as compared to placebo. In addition, ubrogepant 50 mg also showed a statistically significant greater percentage of patients achieving absence of the most bothersome migraine-associated symptom at two hours after the initial dose.

“We are excited about advancing our migraine program with two investigational small molecule oral CGRP receptor antagonists,” said Nicholson. “These are expected to be the first oral CGRP receptor antagonists to market.”

“Antagonism of these receptors reduces pain and the other symptoms of migraine. Atogepant is chemically distinct from ubrogepant, our orally-administered CGRP receptor antagonist for the acute treatment of migraine, with a higher potency and longer half-life, making it suitable for preventive treatment.”

In the CGP-MD-01 study, 844 U.S. adult patients were randomized to placebo, 10-mg once per day (QD), 30-mg QD, 30-mg BID, 60-mg QD or 60-mg twice per day (BID) and treated under double-blind conditions for 12 weeks, for the prevention of episodic migraine. Efficacy analyses were based on the modified intent-to-treat population of 795 patients.

The primary efficacy endpoint was the change from baseline in mean MPM headache days across the 12-week treatment period.

All active treatment groups demonstrated a statistically significant reduction from baseline in the primary efficacy parameter (10 mg QD vs. placebo, p=0.0216; 30 mg QD vs. placebo, p=0.0390; 60 mg QD vs. placebo, p=0.0390; 30 mg BID vs. placebo; p=0.0034, 60 mg BID vs. placebo, p=0.0031).

The reported p-values are adjusted for multiple comparisons by controlling the overall type I error rate of the study at 5 percent, two-sided. Additional details and results from other endpoints are anticipated to be presented at upcoming scientific meetings.

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The reported p-values are adjusted for multiple comparisons by controlling the overall type I error rate of the study at 5 percent, two-sided. Additional details and results from other endpoints are anticipated to be presented at upcoming scientific meetings.

“Allergan anticipates filing of a New Drug Application to the FDA in 2019.”

“We are extremely pleased to share these positive results from atogepant—our first Phase 2b/3 study in episodic migraine—which represent a tremendous opportunity in the prevention of migraine, with a convenient oral dosage form that is currently unavailable.”

David Nicholson, chief research and development officer at Allergan.
Be Boston-bound for erudition in the newest science, technology and techniques in cancer immunotherapy

BY MEL J. YEATES

CAMBRIDGE HEALTHTECH Institute’s Immuno-Oncology Summit once again graces Boston with its sixth annual outing, though this time heading to the Seaport Hotel and World Trade Center. Situated just across Fort Point Channel from downtown Boston, this year’s location is closer to the heart of the city, giving attendees myriad options for food, beverages and entertainment—when they aren’t busy gleaning new information.

So what’s new for the Immuno-Oncology Summit in 2018? Cambridge Healthtech Institute (CHI) notes that the summit now has a track on bispecific antibodies, as well as a new neoantigen-targeted therapies track, which highlights personalized immunotherapy approaches. Immuno-oncology (IO) biomarkers coverage has been expanded to three days in order to cover predictive biomarkers, companion diagnostics and immune profiling, and coverage of adoptive T cell therapy has been expanded to three days to span discovery and development.

With an expanded exhibit hall and a new “Partnering Forum” to highlight emerging companies and investment opportunities, there’s plenty of opportunity to acquire new information, according to CHI, which emphasizes that the annual meeting focuses on the latest applied research.

The conference also offers a wide variety of presentations, seminars and workshops on the newest applications of immuno-oncology, including:

- **Immunomodulatory Therapeutic Antibodies for Cancer**
  - EMERGING TARGETS, COMBINATIONS AND ANTIBODY ENGINEERING FOR NEXT-GENERATION IMMUNOTHERAPY
  - Featured Presentations:
    - “New Immune Checkpoints for Human Cancer Immunotherapy” by Dr. Xingsheng Zang of Albert Einstein College of Medicine
    - “The Development of Agonist OX40 Monoclonal Antibody for Cancer Immunotherapy—Navigating the Bench to Bedside Journey” by Dr. Niranjan Yanamandra of GlaxoSmithKline

- **Rational Combination Cancer Immunotherapy**
  - DATA DRIVES COMBINATORIAL STRATEGIES AND SUCCESSES
  - Featured Presentation:
    - “Rational Combination of Immunotherapy, It Is Science, Not Logic” by Dr. Samir N. Khleif of Albert Einstein College of Medicine

- **Oncolytic Virus Immunotherapy**
  - COMMERCIALIZING THE EXCITING POTENTIAL OF ONCOLYTIC VIROTHERAPY
  - Featured Presentations:
    - “Unlocking the Full Potential of Cancer Immunotherapy” by Dr. David Kim of IGITE Immunotherapy

- **Training Seminar 1**
  - CAR-T ENGINEERING FOR PROTEIN SCIENTISTS
  - Featured Presentations:
    - Dr. Dina Schneider of Lentigen Technology Inc.

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**Aug 27-29**

- **Bispecific Antibodies for Cancer Immunotherapy**
  - ENGINEERING NEXT-GENERATION BIOTHERAPEUTICS IN IMMUNO-Oncology
  - Featured Presentations:
    - “The Immune Force Awakens with Novel Bispecific Biotherapeutics: Challenges and Opportunities” by Dr. Rakesh Dietz of MedImmune
    - “Bispecific Technology for Multiple Avenues of T Cell Activation” by Dr. John Desjarlais of Xencor
    - “Mechanisms of Action for the Application of BiTE Antibodies in Immunotherapy” by Dr. Tara Arvedson of Amgen

- **Preclinical and Translational Immuno-Oncology**
  - PREDICTIVE PRECLINICAL MODELS AND TRANSLATIONAL STRATEGIES FOR CANCER IMMUNOTHERAPY
  - Featured Presentations:
    - “3D Model to Mimic the Microenvironment” by Dr. Litao Zhang of Bristol-Myers Squibb
    - “The Role of Genetically Engineered Mouse Models of Cancer in Profiling Novel Immune Targeting Therapies” by Dr. Elizabeth Hardaker of AstraZeneca

- **Immuno-Oncology Biomarkers 2**
  - PREDICTIVE BIOMARKERS AND COMPANION DIAGNOSTICS
  - Featured Presentations:
    - “Immunophenotyping to Differentiate Responder and Non-Responder Patients in Cancer Immunotherapy” by Dr. George Poste of Arizona State University
    - “Predictive Biomarkers in Colon Cancer and Mismatch Repair Deficient Tumors” by Dr. Robert Andes of Johns Hopkins University

**Aug 28-29**

- **Immunological Biomarkers 1**
  - QUANTITATIVE IMMUNE PROFILING AND IMMUNE MONITORING
  - Featured Presentation:
    - “Exosomes and Their Cargo as Tumor Biomarkers” by Dr. Samir Hanash of MD Anderson Cancer Center

- **Immuno-Oncology Summit**
  - SUMMIT CONTINUED ON PAGE 28

This year’s Immuno-Oncology Summit from Cambridge Healthtech Institute will be held at the Seaport Boston Hotel and World Trade Center.

Be Boston-bound for erudition in the newest science, technology and techniques in cancer immunotherapy

**Cambridge Healthtech Institute’s Sixth Annual Immuno-Oncology Summit**

**August 27–31, 2018**

**Boston, Seaport World Trade Center**
SUMMIT CONTINUED FROM PAGE 27

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.

SUMMIT CONTINUED FROM PAGE 27

hensive five-day, 12-track program covers immunomodulatory antibody engineering, emerging immuno-oncology targets, combination immunotherapy, preclinical and translational IO, predictive biomarkers and companion diagnostics, adoptive T cell therapy, oncolytic viruses and personalized cancer vaccines.

“...The Immuno-Oncology Summit brings together a unique and international mix of large and medium pharmaceutical and biotech companies, leading universities and clinical research institutions, government and national labs, CROs, emerging companies and tool providers—making the summit a perfect meeting place to share experience, foster collaborations across industry and academia and evaluate emerging technologies,” CHI notes of the event. “Now in its sixth year, the IO Summit consistently delivers a cutting-edge agenda, 600-plus senior delegates and a sold-out exhibit hall. Please join us in Boston for comprehensive scientific coverage and unparalleled networking opportunities.” Also among the highlights this year is the plenary keynote session, which kicks off on Tuesday, Aug. 28, at 4:15 p.m. Dr. Jennifer Brogdon, the director of the Exploratory Immuno-Oncology operations at Novartis, will present “CAR-T Therapy for B Cell Malignancies,” followed by “Walking on the Moon: Reflections on the Work of the Cancer Moonshot and the Future of the Biden Cancer Initiative” by Dr. Gregory C. Simon, president of the Biden Cancer Initiative.

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Researchers test a new immunotherapy combo and a pioneering approach to cancer vaccination

BY MEL J. YEATES & JEFFREY BOULEY

SIGNALLING DOUBLE trouble for some cancers, researchers in Augusta, Ga., have paired two immunotherapies together as a novel way to tackle tumors. Specifically, pembrolizumab, which enables the T cells a patient already has to better attack a tumor, and poly-IC, which can produce an independent and vigorous immune response, are being given together for the first time to help more patients wage a stronger war on a wide range of solid tumors, researchers say.

The first phase of the clinical trial of this unique pairing is looking at the safety of combining the two drugs in a dozen patients with solid tumors, like lung or liver cancer, which have not responded to standard therapy. A second phase will commence at its completion in about 30 patients with nonresponsive metastatic colon cancer.

“We have experiments in mice that show that the combined use of PD-1 antibody and poly-IC is synergetic for the recognition of tumors and an antitumor response mediated by T cells,” noted Dr. Esteban Celis, co-leader of the Cancer Immunology, Inflammation and Tolerance program at the Georgia Cancer Center at Augusta University, and Dr. Sharad Ghamande, associate director for clinical research and trials at the Georgia Cancer Center. “Now we want to see if this synergy can help more patients wage a stronger war on a different tumor site to be more effective,” he noted.

The synthetic PD-1 antibody, pembrolizumab, allows those T cells that are already at the tumor site to be more effective, “he noted. The PD-1 antibody blocks the interaction and their interaction inhibits the activity of the T cells that kill tumors, Celis explained.

“The antibody blocks the interaction and allows those T cells that are already at the tumor site to be more effective,” he noted. The synthetic PD-1 antibody, pembrolizumab, allows those T cells that are already at the tumor site to be more effective, “he noted. The PD-1 antibody blocks the interaction and their interaction inhibits the activity of the T cells that kill tumors, Celis explained.

The idea is that tumors that have a lot of mutations are more immunogenic, so that is why they tend to be infiltrated by T cells,” Celis said. “In tumors that are less immunogenic, we hope that poly-IC will make them more immunogenic.”

In other unique immunoncology news—and going “across the pond” to Europe—a signal regimen in a second tumor type demonstrating response of IL-12 platform in breast cancer and glioblastoma

BOSTON—Ziopharm Oncology Inc., a biotechnology company focused on development of next-generation immunotherapies utilizing gene- and cell-based therapies to treat patients with cancer, in June presented clinical data showing the Controlled IL-12 platform as monotherapy achieved antitumor responses in patients with metastatic breast cancer (mBC) and patients with recurrent glioblastoma (rGBM) at the 2018 American Society of Clinical Oncology Annual Meeting. The poster, “Demonstration of Anti-Tumor Immunity via Intratumoral Regulated Platform Ad-RTS-hIL-12 in Advanced Breast Cancer and Recurrent Glioblastoma Patients,” presented data from two open-label trials that evaluated Ad-RTS-hIL-12 plus veledimex, a gene therapy designed to induce and control the expression of the powerful cytokine interleukin 12 (IL-12). Updated data from the company’s Phase 1 rGBM study shows median overall survival (mOS) of 12.7 months has been sustained for patients treated with Ad-RTS-hIL-12 plus 20 mg of veledimex at a mean follow-up time of 12.9 months as of May 4, 2018. This mOS of 12.7 months continues to compare favorably to the five to eight months survival established in historical controls for patients with rGBM.

“We remain excited that Ad-RTS-hIL-12 plus veledimex as monotherapy demonstrates promising antitumor responses and makes cold tumors hot with new immune-infiltrating cells and overexpression of checkpoints,” said Dr. Francois Lebel, Ziopharm’s chief medical officer and executive vice president for research and development. “We look forward to further development of our Controlled IL-12 platform in combination with immune checkpoint inhibitors, with one combination trial initiated in brain cancer and plans to advance a similar treatment regimen in a second tumor type later this year.”
 Commentary: Immuno-Oncology—Gold Rush or a Golden Age?  
BY DR. ANDY KINLEY OF NOVELLA CLINICAL

The last few years saw the success of checkpoint inhibitor drugs like pembrolizumab and nivolumab in cancer and brought on a whole new meaning to the field of immunotherapy. Modulating the immune system to kill tumor cells became a main focus of many drug sponsors and the term “immuno-oncology” became a new buzzword. Estimates show that currently hundreds of clinical trials involving immuno-oncology therapies are being carried out with the recruitment of over a hundred thousand patients.

As excitement builds in the field, concerns have also arisen over poorly designed trials, patient suffering and inefficient use of research funds and patient volunteers. In this commentary, we take a deeper look at the status of the crowded immuno-oncology field and explain how this gold rush (and the scientific world in general) can derive the best benefit from a multitude of clinical trials and the information so gathered.

INTRODUCTION

A feverish hype has surrounded the field of immuno-oncology (IO) over the past decade with the discovery and approval of several checkpoint inhibitors. Keytruda (pembrolizumab), perhaps the most notable checkpoint inhibitor, has been approved for the treatment of melanoma, lung cancer, head and neck cancer and several other cancer types. The concept of cancer immunotherapy is not new, and the beginnings of the field can be traced back to findings made more than a century ago. However, incredible progress has been made recently, and with the success of drugs like Keytruda, which generated greater than $1 billion in sales in the third quarter of 2017 alone, the business case for investments on immuno-oncology therapeutics is clear.

IS IO EXPERIENCING A GOLD RUSH?

Keytruda is one of six FDA-approved checkpoint inhibitors for the treatment of a wide variety of cancers. Due to their market and financial impact, these therapies have become an immunotherapy option for many patients. As we’ve described above, there is certainly a “gold rush” in the field, but it may not be as bad for patients as some have argued. One additional criticism of the excessive attention to IO—known as the “gold rush”—may not be 100-percent accurate. There are many waves of checkpoint inhibitors, either antibodies or small molecules, that “release the brakes” of the immune system by inhibiting molecules which prevent immune attacks against cancer cells (i.e., TIM-3, VISTA, LAG-3, IDO or KIR). Simultaneously, there is also active research into molecules that “step on the gas” by stimulating cellular targets (i.e., CD40, GITR, OX40, CD137 and ICOS) to kill cancer cells.

A GOLD STANDARD

With the hype and activity in the immuno-oncology field increasing, there are sure to be additional successes and failures, adding fuel to the fire for each side of this argument. One thing that both sides can agree on is that clinicians and researchers want clinical trials to be run with solid, scientific rationales that have the greatest potential to benefit patients. As we’ve described above, there is a gold rush in the field, but it may not be as bad for patients as some have pointed out. The activity in this area has helped, and we will continue to help, answer critical research questions and push revolutionary cancer therapeutics to market.

Andy Kinley, Ph.D., is senior director of oncology strategy at Novella Clinical, where he provides strategic guidance to the oncology and operational teams as well as consultative oversight for biopharma sponsors developing cancer therapeutics.

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FIRST CONTINUED FROM PAGE 28

first-of-its-kind treatment vaccine has moved into a Phase 1 clinical trial for patients with multiple myeloma cancer (NSCLC), under a collaboration agreement between Cancer Research UK and Asterias Biotherapeutics Inc. Cancer Research UK will manage the initial development of AST-VACs, which it describes as “a promising immunotherapy candidate derived from a standardized human embryonic stem cell line.”

If shown to be safe and effective, the hope is that AST-VACs could serve as an additional treatment for patients who no longer have advanced disease but whose lung cancer is at high risk of returning. Also, it could possibly be of use in combination with other treatments for patients who have advanced disease.

“This vaccine trial is a pioneering approach to improving treatment for lung cancer, the biggest cause of cancer death worldwide,” said Professor Angela Blackburn, Cancer Research UK’s director of drug development. “By coupling our expertise with a leading biotechnology company, we’ve accelerated the development of this experimental treatment by years.”

The vaccine is made from dendritic cells that are able to “kick-start” the body’s immune system, according to Cancer Research UK—they present antigens on their surface and orchestrate a T cell immune response against cells bearing the same antigen. AST-VACs dendritic cells are engineered to express a modified form of a protein called telomerase, which is almost always present at high levels in various types of cancer cells, but rarely found in healthy cells. This modified form of telomerase, called hTERT, can stimulate a natural immune response targeted at cancer cells. High levels of telomerase are a common feature of many cancers, so AST-VACs has the potential to become an immunotherapy option for other types of cancer beyond NSCLC, according to the collaborators.

Previous dendritic cell therapies have been made using patients’ own cells, but this process is costly, slow and inefficient. By using a pioneering approach of growing mature dendritic cells from a single human embryonic stem cell line in the laboratory, it’s hoped AST-VAC2 will overcome these challenges.

Michael Mulroy, president and CEO of Asterias, commented that: “The experience and expertise of Cancer Research UK’s Centre for Drug Development and Biotherapeutics Development Unit have brought us a step closer to realizing the potential of this exciting experimental treatment ... In the future, there’s also the potential to utilize this novel platform technology to produce treatments that could, in addition to targeting cancer antigens and thereby treat a wide range of different cancers and tumor types.”
**A bifunctional immunotherapy**

Germany’s Merck KGAa presents updated clinical results for M7824 at ASCO meeting

DARMSTADT, Germany—In early June, Merck KGAa—based in Darmstadt, Germany, and traditionally known as EMD in the United States and Canada to distinguish it from Merck & Co.—announced results from expansion cohorts of the ongoing MyRaq Phase I clinical trial program at the American Society of Clinical Oncology (ASCO) 2018 Annual Meeting in Chicago.

These data include results in patients with advanced non-small cell lung cancer (NSCLC) and human papillomavirus-associated cancers, presented in collaboration with the National Cancer Institute, providing further evidence that bringing together a transforming growth factor β (TGF-β) trap with the anti-PD-L1 mechanism may generate clinically relevant antitumor activity.

“M7824’s dual approach to fighting cancer, which brings together a TGF-β trap with the anti-PD-L1 mechanism, complements our existing immuno-oncology portfolio,” said Dr. Luciano Rossetti, global head of research and development at biopharma business of Merck KGaA. “The unique design of this fusion protein offers the potential to optimally engage the TGF-β pathway. This is one example of the creative approaches we are taking to address challenging cancers where we believe we can deliver a transformational change for patients.”

In patients with second-line (no prior immunotherapy) advanced NSCLC from the cohort of the ongoing Phase I clinical trial, signs of clinical activity were seen across PD-L1 expression levels. At the recommended Phase 2 dose (1,200 mg every two weeks), an investigator-assessed confirmed overall response rate of 40.7 percent was achieved.

“T cell infiltration and tumor response in patients with second-line (no prior immunotherapy) advanced NSCLC and human papillomavirus-associated cancers,” said Frederic Ors, CEO of IMV Inc. “IMV’s approach to program T cells to optimally engage the TGF-β pathway and PD-L1 has the potential to offer new treatment options for patients with very limited treatment options.”

“Positive clinical data shared for DeCidE1 vs. ovarian cancer”

HALIFAX, Nova Scotia—June brought news that IMV Inc. shared new positive data in an oral presentation for its DeCidE1 (DPX-Survivac with low-dose Cyclophosphamide) in ovarian cancer. Results are from the DeCidE1 Phase I/II clinical trial at the 2018 American Society of Clinical Oncology annual meeting.

These data from the ongoing Phase Ib/II trial evaluated the safety and efficacy of the combination of IMV’s lead candidate DPX-Survivac and low-dose cyclophosphamide, with Incyte’s IDO1 enzyme inhibitor epacadostat, in patients with advanced recurrent ovarian cancer.

DPX-Survivac consists of survivin-based peptide antigens formulated in IMV’s proprietary DPX drug development platform. DPX-Survivac is believed to work by eliciting a cytotoxic T cell immune response against cells presenting survivin peptides. Survivin, recognized by the National Cancer Institute as a promising tumor-associated antigen, is broadly overexpressed in most cancer types and plays an essential role in antagonizing cell death, supporting tumor-associated angiogenesis and promoting resistance to anti-cancer therapies. IMV has identified over 15 unique indications in which the over-expression of survivin can be targeted by DPX-Survivac.

During the presentation, Dr. Oliver Dorigo, an associate professor of obstetrics and gynecology at Stanford University Medical Center, provided an update on the clinical benefits from the first 18 evaluable participants among 26 enrolled (including 10 from the 100 mg epacadostat dosing cohort and eight from the 300 mg epacadostat cohort), as well as blood sample and tumor biopsy analyses from the study’s first dosing cohort. IMV is conducting the Phase Ib/II trial in an ongoing collaboration with Incyte Corp.

“We continue to be impressed by the safety and efficacy signals we see from this clinical trial, especially in this heavily pre-treated patient population with advanced ovarian disease and very limited treatment options,” said Frederic Ors, CEO of IMV Inc. “We designed DPX-Survivac to program immune cells in vivo to heighten and sustain antitumor T cell responses. Thus, we are especially pleased to be able to demonstrate, for the first time, a clear correlation between partial regressions and T cell infiltration in the tumors.”

At the time of data cut-off, 39 patients were enrolled (including 25 new participants in the 300 mg cohort, with eight evaluable from day 56 first CT scan). Data from the first 18 evaluable patients across both dosing cohorts showed seven tumor regressions, including four partial responses (PR) reported so far (defined as 20-50 percent decrease in tumor lesion size). Study participants generally tolerated treatments well, with no related serious adverse events.

“T cell infiltration showed PRs with significant and durable tumor regressions lasting more than one year. The third patient with T cell infiltration demonstrated progressive disease with evidence of downregulation of the major histocompatibility presentation pathway and significant increases in suppressive markers, both indicative of mechanisms of resistance. "We know how important T cells are to controlling gynecological cancers, particularly in advanced ovarian disease, where it has been estimated that less than 20 percent of patients are responsive to monotherapies like checkpoint inhibitors,” said Dr. Gabriela Nicola Rosu, chief medical officer at IMV Inc. “IMV’s approach to program T cells in vivo is showing promising results that have been able to connect the dots between T cell infiltration and tumor response in these patients, many of whom have rapidly growing tumors. We believe this data is an important milestone toward our goal of significantly increasing the number of individuals able to benefit from immunotherapy treatments.”
Abcam, Shuwen Biotech link up for CDx kits

CAMBRIDGE, U.K. & DEQING, China—Abcam and Shuwen Biotech have signed a memorandum of understanding under which they will jointly apply their expertise in the production of high-quality antibodies and the development and commercialization of companion diagnostic kits.

“Shuwen has a long-standing reputation amongst pharmaceutical companies for companion diagnostic kit development and central lab testing, and Abcam is a recognized leader in quality antibody development. This alliance will undoubtedly further strengthen Shuwen’s capabilities in developing quality companion diagnostic kits especially immunassay kits,” said Jay Z. Zhang, Shuwen’s chairman and CEO. “We have seen continuous advances at all levels in personalized medicine over the past few years and these can only continue through innovative technologies like those that will be born out of joint efforts between Shuwen and Abcam.”

More work on the way for W0101

CASTRES, France—Mid-May saw an extension of the collaboration between Pierre Fabre and Roche to develop a companion diagnostic (CDx) for W0101. The partnership now extends from developing a prototype immunohistochemistry assay as a CDx for W0101 to include the retrospective determination of IGF-1R expression in patients enrolled in a Phase 1/2 clinical study of the compound. W0101 is an antibody-drug conjugate product candidate that targets the insulin-like growth factor 1 (IGF-1) receptor, and is presently being evaluated in a Phase 1/2 clinical study in patients with relapsed/refractory solid tumors.

“It is noteworthy that the IGF-IR antibody used in the diagnostic assay binds a different epitope than the antibody from the therapeutic construct, both developed by Pierre Fabre Research Institute,” said Dr. Alexandre Fassinou, vice president of translational medicine at Pierre Fabre Research Institute.

PROPER PREDICTION IN PROSTATE CANCER

New studies indicate a valid, predictive biomarker for mCRPC

BY JIM CIRIGLIANO

SAN DIEGO—California-based cancer diagnostics development company Epic Sciences Inc. announced in June two promising new sets of data evaluating their assays for the nuclear-localized androgen receptor splice variant 7 (AR-V7) protein in circulating tumor cells as a predictive biomarker for metastatic castration-resistant prostate cancer (mCRPC).

The first of these data sets was presented at the 2018 American Society of Clinical Oncology (ASCO) Annual Meeting from June 1 to 5 in Chicago. The company and its collaborators presented a total of five studies, including more work on the way for W0101.

Mount Sinai researchers use nasal brush test to diagnose asthma

BY LORI LESKO

NEW YORK—Armed with a simple nasal brush, Mount Sinai researchers have identified a genetic biomarker of asthma that can differentiate asthma from other respiratory conditions such as allergic rhinitis, smoking, upper respiratory infection and cystic fibrosis.

Led by clinical and computational scientists in the Department of Genetics and Genomic Sciences, the Icahn Institute for Genomics and Multi-scale Biology and the Department of Pediatrics at the Icahn School of Medicine at Mount Sinai, the research team published its results in the June 2018 issue of Scientific Reports.

In the journal article, Mount Sinai Health System researchers described using a “nasal brushing” technique to collect RNA from the noses of 150 volunteers, 66 of whom had asthma and 24 of whom did not. After those samples were sequenced, machine learning algorithms were used to analyze the data to determine the differences between the RNA of the two groups.

As a result, a 90-gene biomarker was identified that is specific to people with asthma. It is hoped that soon doctors will be able to simply swab the inside of patients’ noses, then analyze the sample to see if the biomarker is present. The next step involves plans for a follow-up study involving a larger sample size.

“Mild to moderate asthma can be difficult to diagnose because symptoms change over time and can be complicated by other respiratory conditions,” Dr. Supinda Bunyavanich, a researcher at the Icahn School of Medicine, states. “Our nasal brush test takes seconds to collect. For time-strapped clinicians, particularly primary care providers at the front lines of asthma diagnosis, this could greatly improve patient outcomes through early and accurate diagnosis.”

Bunyavanich told DDNews that asthma “can be challenging to diagnose given its waxing and waning symptoms. Individuals may not recognize that they have asthma, and individuals may not be symptomatic when they see their doctor.”

“Studies have shown substantial proportions of the population have asthma-like symptoms without being diagnosed with asthma,” she adds. “Some of these people may actually have asthma and would benefit from diagnosis and appropriate treatment.” At the same time, “some of these people may not have asthma and would benefit from knowing asthma is unlikely, thus avoiding unnecessary treatment with asthma medications. Current guidelines recommend incorporat-
The results address an important unmet need for physicians and patients faced with a choice about how to approach treatment of metastatic castration-resistant prostate cancer. “Prior to AR-V7, physician intuition was the primary decision-making strategy in determining a therapeutic sequencing for patients with mCRPC,” Dittamore explains. “Validating nuclear-localized AR-V7 as a predictive test in this decision demonstrates a survival advantage of AR-V7 over physician intuition. The data support that the use of Oncotype DX AR-V7 Nucleus Detect test has the ability to increase patient survival through better decision making.” A specific, predictive biomarker for prostate cancer has been difficult to isolate, with the male patient who was positive for nuclear-localized AR-V7 in our test having a low to zero misclassification rate.

"Our approach was to lead not with the biomarker, but with an important unmet, relevant clinical question,” he tells DDNews. “The clinical question is: ‘Will these patients live longer on chemotherapy?’ The Scher et al. publication validates this—that patients who test positive with the Oncotype DX AR-V7 Nucleus Detect test will live longer on chemotherapy than when treated with AR-V7 inhibitors, abiraterone or enzalutamide. Given the two datasets, the test has been validated in the context of the clinical question being asked.”

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For more information, visit www.DDN-News.com
Grant awarded for continuous modular manufacturing

**BY MEL J. YEATES**

ALNWICK, U.K. — The contract research and development organization Arcinova recently received a grant award of £1.5 million from Innovate UK for the development of new flexible modular manufacturing technologies, a project which is set to demonstrate the operating feasibility of innovative continuous production tools. The goal for Arcinova: establish itself as a world leader in defining continuous modular manufacturing technology for the support of new chemical entities’ development, scale-up and manufacture.

According to Dr. Paul Quigley, head of API development and bioanalytical services at Arcinova, “Arcinova felt that the current Innovate UK funding round for the development of new medicines manufacturing technology offers an ideal opportunity to enhance our technological capabilities...” The initial focus was on the development of new continuous manufacturing technologies, and this was an area of particular importance to Arcinova and an area where the University of Nottingham has particular strengths. Their previous successful track record of collaboration, allied to the skill sets of the Nottingham and Arcinova teams in the area of continuous processing technology development, made this collaboration a natural evolution of the current relationship.

The project, which will span a three-year period, will be undertaken in collaboration with a team led by Prof. Mike George, with Prof. Pete Licence and Prof. Sir Martyn Poliakoff at the University of Nottingham. The aim of the project is to develop a continuous, flexible modular manufacturing technology platform which will enable Arcinova to handle increasingly complex chemistries with more discrete manufacturing steps.

“In response to the development of new and more targeted pharmaceutical treatments, small-molecule drug substances are becoming more complex in nature, more potent and, as a consequence, the drug substance requirements for a candidate drug—both through the clinical development phase and at commercial launch—have reduced significantly,” Quigley notes. “Our vision for this project is the development of a continuous, flexible modular manufacturing technology platform which will enable Arcinova to meet this technological need and to be a leading player in the development, scale-up and manufacture of new small-molecule drugs. Initially, a number of key technology areas will be chosen for development,” continues Quigley. “These areas will be chosen on the basis of expected technical need from Arcinova and on the basis of demonstrated expertise from the academic partner (University of Nottingham).”

“My colleagues and I at Nottingham are firmly convinced that flow chemistry can transform chemical manufacture in the U.K., and this partnership with Arcinova is an opportunity to turn our vision into reality,” added George, a professor of chemistry at the University of Nottingham.

Arcinova will use a grant to help fund development of new flexible modular manufacturing technologies.

The developed continuous modular manufacturing technology reportedly will be easily scalable, with a reduced manufacturing footprint when compared to more traditional batch reactor approaches. The developed technologies will enable Arcinova to enhance manufacturing capacity and minimize inventories for highly reactive hazardous processes whereas for a batch process the reaction scale intensity and product yield, generating high purity materials and with the ability to handle potentially hazardous reactant conditions. Additional requirements would include the need for improved process economics when compared to traditional batch processing conditions, and the ability to minimize process solvents, reagents and catalysts as further drivers,” Quigley tells DDNews.

“Continuous processing technologies offer a solution to this unmet need, yet the technology is still evolving and in many areas (oxidation, thermal processing [high and low] and in solvent reuse) the technologies available are not, as yet, scalable,” he notes. “Arcinova in particular has a need for a technology which could offer the capability to satisfy long-term demand for new chemical entities as drug substances on an existing site footprint without the need to use large chemical reactors, with low inventories and with the ability to offer world-class chemical processing technologies that would differentiate us from the global competitor base and enhance our business growth prospects.”

When asked how the project has been since the announcement of the grant, Quigley says, “The project is going well, with the University recruitment phase in an advanced state. We have good project management discipline in place and regularized meetings to ensure that the project outputs are well managed and metricalized. Our intention is to rapidly apply the developed manufacturing technologies to real case projects which can rapidly enhance Arcinova’s technological competitiveness.”
iPSC interest

FCDI licenses technology from UC Irvine to develop iPSC-derived microglia for neurological disease models

BY KELSEY KAUSTINEN

MADISON, Wis.— Fujifilm Cellular Dynamics Inc. (FCDI), and the University of California, Irvine (UCI) have begun an exclusive patent license agreement centered on UCI technology for deriving microglia from induced pluripotent stem cells (iPSCs). Facilitated through the UCI Applied Innovation offices, the agreement covers the licensing and commercialization of UCI’s technology in the commercial research field, as well as a non-exclusive patent license agreement for commercializing microglia media formulation. Financial details for the deal were not released.

This technology is relatively new, all things considered, having only been detailed in a paper in Neuron in April 2017. Commercial interest from a company like FCDI, which is a market leader in the development and manufacture of human iPSCs and differentiated tissue-specific iPSCs, is an encouraging sign for UCI. FCDI is looking to leverage this technology to produce better models for studying degenerative neurological diseases.

“Until now researchers have relied predominantly on animal models, which do not sufficiently mimic the human disease, to study the role microglia play in neurodegeneration,” said Seinito Satake, chairman and CEO of FCDI. “With UCI’s technology, FCDI will bring to market iPSC-derived microglia that will provide researchers with better tools to characterize microglia from donors with neurological diseases, to develop assays that distinguish between normal and diseased behaviors and to advance efforts in discovering new therapies.”

“We are delighted that FCDI has recognized the importance of iPSC-derived microglia,” said Llewellyn-Davies, chief financial and business officer of FCDI. “The agreement for commercializing microglia from donors with neurological diseases, induced pluripotent stem cells (iPSCs), will bring to market iPSC-derived microglia that will provide researchers with better tools to characterize microglia from donors with neurological diseases, to develop assays that distinguish between normal and diseased behaviors and to advance efforts in discovering new therapies.”

NIH to fund animal testing centers for genome editing

BETHESDA, Md.—The National Institutes of Health recently announced funding for a new program that will establish two large-animal testing centers, one of which will test genome-editing delivery technologies and editors developed by the NIH Somatic Cell Genome Editing program. One center will test the technologies in pigs, and the other in monkeys (specifically rhesus and marmosets). It is expected that the first center will have the capacity to test roughly 250 animals a year as of April 2021, while the second center is expected to test roughly 110 animals per year. The NIH Common Fund Office of Strategic Coordination will provide $2.5 million in fiscal year 2019-2020 and $4.5 million in fiscal years 2021-2023 for this effort. The NIH grant also states that the centers will be expected to “Establish assays and SOPs to evaluate on-target and off-target genome editing in target cells and tissues, including germine cells, in wild-type animals.”

BRIEFS

Biogen to acquire TMS-007

CAMBRIDGE, Mass.—June saw the beginning of an exclusive option agreement between Biogen and TMS Co. Ltd., under which Biogen will acquire TMS-007—a plasminogen activator with a novel mechanism of action that helps to break down blood clots and is thought to inhibit inflammation at the site of thrombosis—and backup compounds. Biogen will pay TMS $4 million up front and $18 million if Biogen exercises its option. TMS also stands to receive up to $135 million in potential development and commercialization milestones, as well as tiered royalties. TMS-007 has reduced infarct volume (dead tissue due to lack of blood supply) in rodent and primate models of embolic and thrombotic stroke. A double-blind, placebo-controlled Phase 2 study is underway to determine the safety and efficacy of a single intravenous administration up to 12 hours after stroke onset in patients with acute ischemic stroke.

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IN THIS SECTION

Animal testing/Genetics
NIH to fund animal testing centers for genome editing.................................. 35

License and acquisition deals
Biogen to acquire TMS-007.................................................. 35

Strengthening its immunology portfolio........................................... 35

Neurology/Stem cells
iPSC interest....................................................... 35

Startups
2 Hills launches with $2M SBIR grant........................................ 36

Tools and technology
On the cutting edge.................................................. 35

STRENGTHENING ITS IMMUNOLOGY PORTFOLIO

Apeiron signs licensing deal for new checkpoint inhibitor with the Medical University of Vienna and IMB

BY DONNIE STAFF

VIENNA—Apeiron Biologics AG, a clinical-stage company focused on cancer immunotherapy, announced near the end of June the signing of an agreement with the Institute of Molecular Biotechnology GmbH (IMBA) of the Austrian Academy of Sciences and the Medical University of Vienna. The agreement grants Apeiron an exclusive worldwide license to a novel technology targeting casitas B cell lymphoma-b (Cbl-b). Cbl-b is an intracellular checkpoint limiting the immune reactivity in various immune cells, such as T cells and natural killer cells, and was originally discovered by Dr. Josef Penninger, scientific director of IMBA.

According to Apeiron, inhibiting Cbl-b not only distinctly activates immune cells but offers the opportunity to deactivate other relevant checkpoints—including CTLA-4 and PD-L1/PD-1—and thus can be regarded as the “master checkpoint” in cancer immuno-

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Speaking of a deal between his company and the Medical University of Vienna, Peter Llewellyn-Davies, chief financial and business officer of Apeiron, said: “The agreement expands our portfolio of immunotherapies targeting Cbl-b and is also an excellent example of an academic-industrial partnership maximizing the strengths of both parties.”

Apeiron is engaged in an innovative cellular immunotherapy project based on the knockdown of Cbl-b (APN401), which	

CONTINUED ON PAGE 36
An additional $4 million in seed capital will help new company pursue novel cancer therapeutics

BY DDNEWS STAFF
HOUSTON—7 Hills Pharma, a privately-held immunotherapy company focused on development of novel tumor-targeting cell adhesion agents, announced today that it has been awarded a $2 million Small Business Innovation Research (SBIR) grant by the National Institutes of Health (NIH).

This is the second NIH grant awarded to the company for the advancement of its integrin activator. The first grant supported the successful completion of the proof-of-concept study. The SBIR award is based on a competitive federal grant program aimed at supporting scientific excellence and technological innovation. The NIH grant is in addition to $4 million in seed capital provided to 7 Hills from private investors.

“We are honored by the NCI’s support of our important work in making tough-to-treat, non-immunogenic solid tumors more susceptible to antitumor attacks by the immune system and check point inhibitors,” said Dr. Upendra Marathi, president and CEO of 7 Hills. “With this funding and the financial support from our angel investors, we plan to conduct key IND-enabling preclinical studies for our lead compound; HP349 and related compounds for the treatment of drug resistant tumors with defective T cell-tumor cell adhesion.”

“The fundamental problem in disease progression with cancer is that solid tumors evade the immune system by preventing the infiltration, function and ultimate attack of T cells and other tumor-associated immune cells,” said Dr. Darren Woodside, co-founder of 7 Hills and chairman of the NIH Innovative Immunology Research Study Section. “It’s an adhesion problem. We have known that solid tumors create an immunosuppressive microenvironment that prevents killer T cells from adhering to the tumor blood vessel lining and working their way into the tumor to do their job. 7 Hills is optimizing novel integrin activators to address and reverse the inherent tumor protective environment, promoting T cell destruction of the tumor while maintaining a favorable overall safety profile by leveraging the natural biological mechanism of integrins.”

Fujifilm Cellular Dynamics Inc. (FCDI) is looking to leverage a technology for deriving microglia from iPSCs, with the aim to produce better models for studying degenerative neurological diseases. Pictured here is FDCI’s parent company, Fujifilm.

Microglia play an important role in Alzheimer’s and other diseases of the central nervous system. Recent research has revealed that newly discovered Alzheimer’s risk genes influence microglia behavior. Using these cells, we can understand the biology of these genes and test potential new therapies,” Blurtom-Jones explained at the time.

Details of this technology appeared in the 2015 Neuron paper titled “iPSC-derived Human Microglia-like Cells to Study Neurological Diseases.” As noted in the abstract, “We find that iMGLs developed in vitro similarly to microglia in vivo, and whole-transcriptome analysis demonstrates that they are highly similar to cultured adult and fetal human microglia. Functional assessment of iMGLs reveals that they secrete cytokines in response to inflammatory stimuli, migrate and undergo calcium transients and robustly phagocytose CNS substrates. iMGLs were used to examine the effects of AB fibrils and brain-derived tau oligomers on AD-related gene expression and to interrogate mechanisms involved in synaptic pruning. Furthermore, iMGLs transplanted into transgenic mice and human brain organoids resemble microglia in vivo.”

“We are pleased that FCDI has licensed our protocol to make and distribute microglia to the scientific community. As leaders in the field of providing iPSC-derived products, we are confident that FCDI will provide researchers and scientists with a reliable product in large scale to carry out quality studies,” Wayne Poon and Edsel Abud, UCI co-inventors of the technology, said of the recent licensing deal. This isn’t the first iPSC-focused deal for Fujifilm Corp, so far this year. In February, the company launched a collaboration with Takeda Pharmaceutical Co. Ltd. for the development of regenerative medicine therapies using iPSC-derived cardiomyocytes to treat heart failure.

Takeda gains a “right of first negotiation” to collaboratively and globally commercialize regenerative medicine products featuring iPSC-derived cardiomyocytes currently being developed by FCDI. The companies will work together to investigate the safety and efficacy of any produced therapies. While no specific financial details were disclosed, Takeda will make a one-time payment to Fujifilm.

APEIRON

CONTINUED FROM PAGE 35

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Michael Krebs, managing director of IMBA added: “We at IMBA see ourselves as an important player in the value chain of biomedical innovations. The IMBA is developing completely new approaches for the treatment of human diseases and thereby enabling potentially alternative treatment options for patients. This collaboration with Apeiron shows once again that it is worthwhile for the Austrian government to invest in science and that the geographical proximity of excellent academic and business institutions, as can be found at the Vienna BioCenter, represents a promising business model.”
Turning data into action for clinical and translational genomics research
RIJSWIJK, Netherlands & CAMBRIDGE, Mass.—Bluebee Corp. announced in May the release of BLUEBASE, a complete data management solution designed to transform next-generation sequencing (NGS) and metadata into actionable genomic knowledge with efficiency and clinical-grade security. BLUEBASE runs on the Bluebee core data analysis platform and provides post-sequencing intelligent data aggregation, ease of querying and deep knowledge mining. BLUEBASE is aimed at diagnostic assay developers, pharmaceutical researchers, clinical trial operators and investigators of population-scale initiatives, offering a turnkey solution to efficiently realize clinically-relevant information from large-scale genomic data.

BLUEBASE aggregates, organizes and stores combined genomic data sets, phenotypes and other metadata from a vast ecosystem of curated public and private databases. With a customizable data model, BLUEBASE accommodates a wide scope of user-defined metadata and ontology frameworks, including the integration of a dynamic public knowledge base of 130 data sources and hundreds of millions of data records, composed of publications, variant datasets, clinical studies and other data sources. Private data sets and metadata are said to be easily integrated within the system.

A range of applications are enabled by BLUEBASE, including discovery and validation of biomarkers, insight into patient stratification approaches, cross-study analyses by multidisciplinary teams, identification of drug candidates for clinical trials and more. Having data mined and readily accessible in BLUEBASE within the Bluebee platform reportedly eliminates data redundancy and risks associated with physically transferring data. BLUEBASE is designed to be easily integrated within the system.

“BLUEBASE was created as part of our mission to further serve precision medicine initiatives,” says Hans Cobben, CEO of Bluebee. “As part of the Bluebee platform, volume to value from genomic data is now achievable, with high efficiency and clinical-grade security.”

Discovery in real time with NLP
CAMBRIDGE, U.K. & BOSTON—Linguamatics, a leading natural language processing (NLP) text analytics provider, in May announced the latest release of its I2E AMP platform to automate the discovery of critical insights from text using NLP. The I2E Asynchronous Messaging Pipeline (AMP) platform reportedly delivers high-throughput, fault tolerant workflow management for real-time document and record processing, addressing the NLP text mining and ETL (extract transform load) requirements for healthcare and life-sciences organizations of all sizes by allowing users to plug I2E into enterprise workflows and rapidly process streams of data at scale.

“I2E’s flexible NLP platform goes far beyond traditional entity mark-up, providing semantically enriched data that normalizes concepts and relationships based on the relevant context,” said David Milward, chief technology officer for Linguamatics. “With AMP, clients now have an enterprise class, high-throughput solution that provides secure, fault-tolerant, scalable and real-time ETL from unstructured text to structured data.”

“AMP provides for the rapid transactional processing of unstructured data for a variety of workflows, including document markup and data extraction to feed enterprise search engines, machine learning, data warehouses and dashboards,” said Phil Hastings, chief business development officer for Linguamatics. “The 2.0 release includes new options that make it an even more valuable solution that can be applied to multiple use cases across life sciences and healthcare.”

Shuzo Maruyama, a general manager at Shimadzu
Shimadzu enhances MS platform with new Q-TOF System
COLUMBIA, Md.—In other recent tools and technology news, Shimadzu announced the launch of the quadrupole time-of-flight (Q-TOF) LCMS-9030 system. The Shimadzu LCMS-9030 is a research-grade mass spectrometer designed to deliver high-resolution, accurate-mass detection with incredibly fast data acquisition rates, allowing scientists to identify and quantify more compounds with greater confidence.

Ultra-fast (UF) acquisition rates and core ion beam technologies developed for the triple quadrupole platform are said by the company to have created new possibilities in quantitative mass spectrometry by delivering exceptional sensitivity, specific quantitation and enhanced target compound verification. Also in the new system, core ion beam technologies transition toward a unique approach in ion gating using UAccumulation to create a precise pulse of ions into the flight tube optimized for high sensitivity and high resolution using iReTOF reflectron technology. The iReTOF generates an ideal reflectron field, delivering the highest resolution for the flight path with highly stable mass accuracy.

“Our Q-TOF technology on the LCMS-9030 will push the boundaries further for high mass accuracy and high mass resolution detection and will make an impact across all applications, from small molecule quantitation to complex intact protein analysis,” said Shuzo Maruyama, general manager of the Analytical & Measuring Instruments Division at Shimadzu.
LONDON—Scientists have discovered that tumorous cells in an aggressive type of childhood brain tumor work together to infiltrate the brain, and this finding could ultimately lead to much-needed new treatments, according to a new study titled “Functional diversity and cooperativity between subclonal populations of pediatric glioblastoma and diffuse intrinsic pontine glioma cells” and published in Nature Medicine at the end of June.

In the study, funded by Cancer Research UK with support from Albie’s Army and the DIPG Collaborative, the researchers investigated a type of childhood brain tumor called diffuse intrinsic pontine glioma (DIPG), shining a light on its most aggressive characteristic—it’s ability to leave the brain stem and send cancer cells to invade the rest of the brain. DIPG is incredibly difficult to treat, and nearly all children with this type of cancer die within two years.

The researchers, led by a team at The Institute of Cancer Research in London, used donations of biopsy tissue and the brains of children who had died as a consequence of DIPG to look deep into the tumor and learn more about its cells.

They found that DIPGs are heterogeneous, meaning they are made up of more than one type of cell. This enables the cells to work together to leave the original tumor and travel into the brain. The scientists say this shows how complex the genetic make-up of the disease is and that a multipronged attack is likely to be necessary for treatment.

As of yet, there is no cure for this illness. Children usually can’t have surgery because of the tumor’s location in the brain stem, which controls functions such as breathing, heart rate, blood pressure and swallowing. Moreover, other treatment options such as chemotherapy don’t work because of difficulty in getting the drugs into the brain, and many DIPG tumors have a resistance to chemotherapy.

“This is the first time we’ve observed this sort of interaction between different tumor cells in DIPG,” said Prof. Chris Jones, who led the study at The Institute of Cancer Research. “The idea that the cells are working together to make the disease grow and become aggressive is new and surprising. Childhood cancers were thought to be very simple, but this shows us that isn’t always the case. Crucially, this gives us hope that we can develop new treatments.”

The study also shows that even cells that exist in relatively small numbers in DIPG can exert a profound influence by leading cells from the main tumor into the rest of the brain to stimulate tumor growth and infiltration. In the case of one kind of cell, as it migrates it releases a chemical messenger called CXCL4, which has the effect of calling other cells from the tumor to follow it.

The next stage of research will see the researchers looking for treatments that target the most important subpopulations of cells in the tumor and/or interfere with the cooperation between cells.
TALLAHASSEE, Fla.—More than two years after reports of skyrocketing Zika rates surfaced worldwide, questions still loom about this complicated virus—but Florida State University researchers think they have an answer.

Does Zika virus suppress the body’s natural barriers against infections by mosquitoes and their genetic material? Does it enter the body, researchers found.

“We were really looking at one specific aspect,” Tang said. “They’re hitching a ride on macrophages to other parts of the body.” Furthermore, Tang said, it appears that the Zika virus is actively suppressing the macrophage’s ability to carry out its typical duties in fighting disease.

“Many viruses get to more sites because of the ability to disseminate through the body better than Dengue?” Tang and Lang found Zika has a unique ability to ferry the virus throughout the body when most viruses would be stopped, and that seems to be due to a specific type of immune cell: the macrophage. Macrophages float throughout the bloodstream and when a virus invades, they typically flock to the site of the disease to fight it. This is the case in Dengue as well as many other invasions, but it’s not what happens when Zika enters the body, researchers found.

Researchers grew macrophages 

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Dr. Hengli Tang of Florida State University

from stem cells in Tang’s lab. Then which results are to either the Zika virus or the Dengue virus. The macrophages were then subjected to a test that measured the mobility of the infected cells. In the Dengue experiment, the macrophages were essentially immobilized as they stayed in one spot to fight the infection. The ones infected with Zika virus, however, maintained their ability to migrate on glass slides.

That could be why the Zika virus is so effective, Tang said, noting: “They’re hitching a ride on macrophages to other parts of the body.”

Broad and Bayer launch new efforts against heart failure

CAMBRIDGE, Mass.—The Broad Institute of MIT and Harvard has teamed up with Bayer to launch the Precision Cardiology Laboratory (PCL), a new endeavor that will pursue scientific insights aimed at developing new therapies for heart failure. According to the American Heart Association, more than 900,000 people are diagnosed with heart failure every year in the United States. The condition, which results from the failure of the heart to pump enough blood, is one of the most common reasons for hospitalization among adults. There are many causes of heart failure, and the PCL will use new tools and methods to more fully understand and treat them.

Research in the PCL will bring scientists from both organizations into an integrated work space at the Broad Institute, effectively combining Broad’s innovative methods for basic scientific discovery and the clinical expertise of its practicing physician-researchers with Bayer’s long history of drug development. The effort will be led by Broad Associate Member Patrick Ellinor, who directs the Cardiac Arrhythmia Service at Massachusetts General Hospital and is a professor of medicine at Harvard Medical School.

The PCL’s initial goal is to develop high-resolution, single-cell maps of cardiovascular tissues in human and animal models. Using tissue samples donated by healthy individuals as well as people suffering from cardiovascular disease, researchers will build datasets to accelerate insights into heart failure.

“Such high-resolution maps of cells and tissues will be a profound asset for understanding heart failure and for developing new and better drugs,” said Ellinor. “I am extremely excited by the potential of this expanded partnership to benefit patients.”

The Broad-Bayer partnership began in 2013 with an oncology program. In 2015, the organizations launched a cardiovascular-specific collaborative effort aimed at using genomics to better understand cardiovascular disease. Now, the led by Deinove and its subsidiary Deinobiotics, is supported by the Investments for the Future Program. It aims to discover new antibiotics by systematically exploring the potential of living systems—specifically, the great diversity of microorganisms.

As the holder of one of the largest bacterial strain banks in the world, bioMérieux, which specializes in the diagnosis of infectious diseases, will provide Deinove with more than 250 strains representing 130 different species. Deinove and bioMérieux have jointly selected the strains for this project targeting a biological diversity. While most current research focuses on a small number of known strains, Deinove has structured its AGIR program around the exploration of an extensive and diverse range of bacteria. Capitalizing on its technology allowing it to automate and accelerate the analysis of large quantities of strains, Deinove aims to maximize the potential of this expanded partnership to benefit patients.

The AGIR project, operated by Bifrance, is carried out by the Deinove Group together with the Charles Virotte Institute, a joint lab aiming to develop innovative strategies for the discovery of new antimicrobials—antibiotics and antifungal agents—through an integrated and automated approach. Its objective is to develop new technologies to optimize the platform for selecting, identifying and developing new antimicrobial molecules of natural origin.

APTO-253 can resume hematologic cancer trial

SAN DIEGO & TORONTO—June 29 saw AptoScience Inc. announce that the U.S. Food and Drug Administration had lifted the clinical hold on APTO-253, AptoScience’s investigational drug for hematopoietic malignancies. APTO-253 is said to be the only known clinical-stage molecule that has the potential to directly inhibit expression of the MYC oncogene, shown to be a causative factor in many malignancies, including acute myeloid leukemia.

Up to 15 clinical centers are expected to participate in the Phase 1b trial, and the screening and dosing will resume as soon as practicable for patients with relapsed or refractory AML or with high-risk myelodysplastic syndromes. Recent data also highlight the role of MYC gene dysregulation in B cell malignancies, and AptoScience hopes to pursue this patient population in the coming months.

The Phase 1b trial of APTO-253 had been placed on clinical hold as a consequence of an event that occurred at a clinical site with the infusion procedure. Ultimately, a root cause investigation determined that the event resulted from chemistry- and manufacturing-based issues, all of which were incorporated into a chemistry, manufacturing and control amendment to the Investigational New Drug application.

“We are eager to return APTO-253 back into the clinic,” said Dr. William G. Rice, chairman, president and CEO of AptoScience. “Our understanding of this molecule has evolved dramatically, and we are excited to deliver a MYC gene expression inhibitor to patients with debilitating hematologic malignancies.”

A new collaboration to discover new antibiotics

MONTPELLIER, France—Deinove, a biotech company that discovers, develops and produces high-value compounds from rare bacteria, has announced a collaboration with bioMérieux, a major player in the diagnostic market, to explore new strains and multiply opportunities to discover new antibiotics. The AGIR (Antibiotics Against Resistant Infectious Germs) program, the opportunities for discovering new antibiotic structures.

“For more than 55 years, bioMérieux has taken forward the diagnosis of infectious diseases to improve patient care. We are very pleased to share our deep expertise in diagnostic tools and microbiology with bioMérieux to support discovery of new antibiotics. Given the threat to public health represented by the rise in bacterial resistance, the search for new treatment options is essential and we are proud to be involved,” said Marie-Françoise Gros, medical director of bioMérieux.

Added Emmanuel Petitot, CEO of Deinove, added: “This is a new example of our approach that aims to explore, as widely and as quickly as possible, the diversity of the living world, thanks to the power of our platform. Working with bioMérieux, one of the leading infectious disease experts, is truly exciting for us.”

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