Investigating an IL-6 antibody
An update on Sanofi and Regeneron’s Kevzara trial in hospitalized COVID-19 patients

BY MEL J. YEATES

PARIS & TARRYTOWN, N.Y.—At the end of April, Sanofi S.A. and Regeneron Pharmaceuticals Inc. announced preliminary results from the Phase 2 portion of an ongoing Phase 2/3 trial evaluating Kevzara (sarilumab), an interleukin-6 (IL-6) receptor antibody, in hospitalized patients with severe or critical respiratory illness caused by COVID-19.

The randomized Phase 2 portion of the trial compared intravenously administered 200 mg of Kevzara, 400 mg of Kevzara and placebo. The trial assessed 457 hospitalized patients who were categorized at baseline as having either severe illness (28 percent), critical illness (49 percent) or multi-system organ dysfunction (23 percent). Patients were classified as severe if they required oxygen supplementation without mechanical or high-flow oxygenation, or were classified as having either severe or critical respiratory illness caused by COVID-19.

Managing macrolactones

New database could aid large-molecule drug discovery and research

BY JEFFREY BOULEY

RALEIGH, N.C.—Small molecules dominate so much of drug discovery research efforts that we don’t get to highlight the larger ones nearly enough in the pages of DDN. So it was welcome news from researchers at North Carolina State University (NC State) and Collaborations Pharmaceuticals when they reported that they have created a free-to-use database of 14,000 known macrolactones—large molecules used in drug development—that contains information about the molecular characteristics, chemical diversity and biological activities of this structural class.

Macrolactones are molecules with at least 12 atoms composing their ring-like structure. Among many useful characteristics, macrolactones’ ability to bind to difficult protein targets makes them suitable for antiviral, antibiotic, antifungal and antiparasitic drugs. However, their size and complicated structure make them difficult to synthesize.

The new database, called MacrolactoneDB, fills a knowledge gap concerning these molecules and could serve as a useful tool for future drug discovery.

“Macrolactones are titanic molecules; macro continued on page 9

KNOW YOUR ENEMY

Team uses knowledge of how SARS-CoV-2 infects cells to identify drugs that could combat it
BY KELSEY KAUSTINEN

SAN FRANCISCO—“Fighting fire with fire” is a well-known idiom, and the research community is taking it to heart in the face of COVID-19 as organizations team up to combat a global pandemic with global collaboration. One such effort has united researchers from the University of California, San Francisco (UC San Francisco), Gladstone Institutes, Icahn School of Medicine at Mount Sinai and Institut Pasteur in an effort to identify existing or pending drugs that could be repurposed to combat SARS-CoV-2. The study was led by Dr. Nevan Krogan, director of the Quantitative Biosciences Institute at UC San Francisco and a senior investigator at Gladstone Institutes.

“While a large amount of COVID-19 therapeutic development research focuses on the antivirals and vaccines, we’ve taken a different approach, targeting the human counterparts and vulnerabilities required for viral infection in a human cell,” said Krogan. “Our work leverages approved and development-stage molecules and will help to focus clinical trials toward the most promising agents to combat COVID-19. We also continue to search for additional agents that target the human proteins used by SARS-CoV-2 to expand the armamentarium against the virus.” The team began by creating a “blueprint” for future drug discovery.

“Macrolactones are titanic molecules; macro continued on page 9

Researchers created a "blueprint" of more than 300 proteins that SARS-CoV-2 takes advantage of to infect and replicate in human cells, then searched for drugs under development and on the market that targeted those proteins. FOR VIRTUAL BACKGROUND USE ONLY. KROGAN
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.

Visit www.ddncancer.com today and every day you need to know more about the world of oncology.
For more information, visit www.DDN-News.com

MARKET NEWS

JUNE 2020 || DDNEWS 3

FUNDING HOPES SPRING ETERNAL

NEW YORK—In a recent report about the market for Clostridium difficile treatment, Persistence Market Research (PMR) notes that it was valued at $840 million in 2018 and is expected to show a compound annual growth rate of 5 percent for the forecast period of 2019 to 2029.

PMR noted that increasing incidence of C. difficile infection fuels the demand for the strengthening of R&D programs, and the critical need for non-antibiotic alternatives for prophylaxis and treatment of such infections is shaping the market landscape.

In fact, according to PMR, the launch of monoclonal antibody drugs for treatment of C. difficile infection and counteractive action for recurrent infection has begun to shift the focus away from antibiotics, with the firm noting, “This new class of drugs represents a breakthrough and will create an extreme challenge for conventional antibiotic medicines.”

The company also announced its lead program targeting satiety circuits for weight loss, with clinical testing expected to begin later this year. A second program targeting gut barrier function, with potential relevance for inflammatory bowel disease and several other diseases, is anticipated to enter the clinic soon after. In addition, the company continues to advance a broad portfolio of programs for gastrointestinal, central nervous system and inflammatory disorders.

“Kallyope pursues programs where the company’s platform provides an edge over other approaches and where we have an opportunity to deliver major clinical benefits rather than incremental improvements over current treatments,” said Kallyope CEO Nancy Thornbery. “We are targeting neural and hormonal circuits, involving in a broad array of physiology and disease.”

$80 million for Pandion

CAMBRIDGE, Mass.—In additional early-spring funding news, Pandion Therapeutics Inc., a clinical-stage, privately held biotechnology company developing modular protein therapeutics for autoimmune disease, announced that it had closed an $80 million Series B financing.

“This financing from a world-class syndicate of life-science investors speaks to the strong potential of the Pandion platform and its potential to transform the treatment of autoimmune disease,” said Paul Cranz, CEO of Pandion Therapeutics. “We believe that our platform, which can be applied to a wide range of autoimmune diseases, has the potential to change the course of these diseases and improve the lives of millions of patients.”

At BioLegend, we know how critical it is to find a solution to the coronavirus pandemic. We are committed to supporting the entire scientific community in their efforts to overcome SARS-CoV-2 and COVID-19 by developing diagnostic tests, therapeutics, and vaccines.

We are working closely with experts across the scientific and medical communities to advance testing and treatment. We are ready to collaborate with you. Please let us know how we can support your research.

biolegend.com

Our reagents are currently being employed to:
- Characterize the immune response
- Develop and validate viral detection kits
- Monitor therapeutic response and vaccine candidates
- Discover virus-associated host biomarkers

BioLegend is ISO 13485:2016 Certified
biolegend.com

As fellow scientists, we know how critical it is to find a solution to the coronavirus pandemic. We are committed to supporting the entire scientific community in their efforts to overcome SARS-CoV-2 and COVID-19 by developing diagnostic tests, therapeutics, and vaccines.

We are working closely with experts across the scientific and medical communities to advance testing and treatment. We are ready to collaborate with you. Please let us know how we can support your research.

biolegend.com

biolegend.com

Let us shoulder the weight with you

COVID-19 is weighing on everyone
COVID-19 clinical trials exhibit encouraging results

LONDON—As of mid-May, 21 ongoing COVID-19 clinical trials had reported interim results, out of which 16 showed positive early results, according to data and analytics company GlobalData.

Scotty Chung-Siu, a senior analyst at GlobalData, noted that 69 percent of these trials are in Phase 1 or 2 right now, and the “majority of them are investigating different drugs, either alone or combination treatments, with one using a secondary intervention. The four multinational clinical trials that are planning to enroll the most subjects are investigating remdesivir, sarilumab and bevacizumab. One of the drugs that recently had positive clinical trial results is remdesivir.”

Most of these trials started in 2020, just after the news broke about the novel coronavirus. These trials have an estimated end date between April 2020 and March 2021. The trials reported a 31 percent faster recovery time over those who received placebo. In addition, the recovery time was 11 days for patients who were treated with remdesivir, compared to 15 days for placebo.

While there are positive signs for many trials, GlobalData acknowledged that not all of the drugs have demonstrated positive results. Hydroxychloroquine, for example, has recently failed to meet endpoints and saw adverse events in a retrospective study. Moreover, the patients treated with hydroxychloroquine had a higher mortality rate. Nonetheless, the number of clinical trials investigating hydroxychloroquine or chloroquine as a primary or secondary drug continues to expand.

In addition, two clinical trials have shown early negative results for efficacy and safety. One is a Phase 3 clinical trial evaluating the efficacy and safety of darunavir and cobicistat in the treatment of COVID-19 pneumonia; the other is a Phase 2 clinical trial to evaluate the safety and efficacy of chloroquine for the treatment of hospitalized subjects with severe acute respiratory syndrome. Both interventional trials have the same expected end date of Aug. 31.

“While many of the current COVID-19 clinical trials show promising early results, conclusions can only be drawn once the final data are reported. With 597 planned clinical trials, there will be more data to draw insights in the coming months,” Scotty Chung-Siu, a senior analyst at GlobalData.

Details of Ongoing COVID-19 Clinical Trials that Reported Positive Interim Results

<table>
<thead>
<tr>
<th>Trial Phase</th>
<th>Primary Drug(s)</th>
<th>Secondary Drug(s)</th>
<th>Trial End Date</th>
<th>No. of Subjects Planned</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>remdesivir</td>
<td></td>
<td>01-May-2020</td>
<td>600</td>
</tr>
<tr>
<td>Phase II</td>
<td>lopinavir/r</td>
<td></td>
<td>01-May-2020</td>
<td>600</td>
</tr>
<tr>
<td>Phase III</td>
<td>azithromycin</td>
<td></td>
<td>01-May-2020</td>
<td>600</td>
</tr>
<tr>
<td>Phase IV</td>
<td>dexamethasone</td>
<td></td>
<td>01-May-2020</td>
<td>600</td>
</tr>
</tbody>
</table>

Source: GlobalData

“While many of the current COVID-19 clinical trials show promising early results, conclusions can only be drawn once the final data are reported. With 597 planned clinical trials, there will be more data to draw insights in the coming months.” Scotty Chung-Siu, a senior analyst at GlobalData.

Details of Ongoing COVID-19 Clinical Trials that Reported Positive Interim Results

<table>
<thead>
<tr>
<th>Trial Phase</th>
<th>Primary Drug(s)</th>
<th>Secondary Drug(s)</th>
<th>Trial End Date</th>
<th>No. of Subjects Planned</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>remdesivir</td>
<td></td>
<td>01-May-2020</td>
<td>600</td>
</tr>
<tr>
<td>Phase II</td>
<td>lopinavir/r</td>
<td></td>
<td>01-May-2020</td>
<td>600</td>
</tr>
<tr>
<td>Phase III</td>
<td>azithromycin</td>
<td></td>
<td>01-May-2020</td>
<td>600</td>
</tr>
<tr>
<td>Phase IV</td>
<td>dexamethasone</td>
<td></td>
<td>01-May-2020</td>
<td>600</td>
</tr>
</tbody>
</table>

Source: GlobalData
Roche becomes founding partner of next phase of BaseLaunch

BASEL, Switzerland—BaseLaunch, an incubator and accelerator that helps “scientists and entrepreneurs launch exceptional biotech companies,” announced in mid-May that Roche has become a founding partner in the next phase of its company-building activities.

BaseLaunch is operated by Basel Area Business & Innovation. During its first phase (2017-2019), BaseLaunch was initially supported by Roche, Novartis Venture Fund, Johnson & Johnson, Pfizer and Roivant Sciences.

Now the second phase is gearing up with new commitments, so the news of Roche as the first partner to be announced for this phase is not just a fresh commitment, but a reaffirmation of the company’s previous partnership with the incubator. BaseLaunch says that additional partners will be made public over the coming months.

“The support of our highly experienced partners will allow BaseLaunch to build on the success of recent years as we look to a sustainable future supporting the development of cutting-edge therapeutic ventures.”

Neil Goldsmith, director of strategy at BaseLaunch

As part of the continuation and growth of the incubator/accelerator, BaseLaunch has increased the funding available per venture to $500,000 to support early-stage innovation. Also, it will now accept applications year-round, rather than just once per year.

During 2018 and 2019, BaseLaunch supported nine early therapeutic ventures that have raised a total of more than $100 million in equity capital from U.S. and European venture funds. Recently, BaseLaunch reported that it had added another four ventures to its portfolio, also noting that the program was instrumental in contributing to the development of six more ventures in the Basel area.

In addition to financing support, BaseLaunch helps build out companies and teams from inception to a point where they can raise financing and enter strategic collaborations. Interested groups can find information at www.BaseLaunch.ch/apply/.

CREDIT: ROCHE

Roche is the first partner to be announced in the second phase of incubator and accelerator BaseLaunch which, like the pharma giant itself, is based in Basel, Switzerland.
Complementary cancer collaboration

Exscientia and SRI combine strengths for oncology drug discovery

BY ILENE SCHNEIDER

MENLO PARK, Calif. & OXFORD, U.K.—Drug discovery is a key element of the production of new medicines, but it can be an incredibly lengthy and expensive process, taking an average of five years. A new collaboration will use two organizations’ proprietary technologies to accelerate the discovery of selective molecules while aiming at a high-value oncology target.

Exscientia, a clinical-stage artificial intelligence (AI) drug-discovery company in the U.K., and SRI International (SRI) entered into a drug-discovery collaboration agreement in May. Under the terms of the agreement, the companies will implement a new approach to drug discovery by integrating AI design with automated compound synthesis. Specifically, the companies will combine SRI’s fully automated SynFinI synthetic-chemistry system with Exscientia’s Centaur Chemist AI platform to automate the design, reaction screening and optimization of new molecules to accelerate the discovery of selective molecules.

Arrakis partners with Roche

Collaboration will use RNA-targeted small-molecule discovery platform for multiple targets

BY DDN STAFF

WALTHAM, Mass.—Early April saw Arrakis Therapeutics, a biopharmaceutical company pioneering the discovery of a new class of small-molecule medicines that directly target RNA, announced a strategic collaboration and license agreement with Roche for the discovery of RNA-targeted small-molecule (rSM) drugs against a broad set of targets across all of Roche’s research and development areas.

“We are excited to partner with Roche’s strong research and development teams. Together, we share a common vision of accessing new drug targets at the RNA level and thereby discovering novel medicines to treat diseases with high unmet medical need. The collaboration will increase the number of new treatments for patients arising from our proprietary rSM discovery platform,” said Dr. Michael Gilman, CEO of Arrakis. “In addition to the Roche collaboration, we are further building our capabilities and advancing our wholly owned rSM programs for diseases unaddressed by today’s medicines.”

Under the terms of the agreement, Arrakis will lead discovery and research activities for each target to a defined point, at which time Roche will have the right to exclusively pursue...
and explore how they might work together would be to embark upon a real project with real-life goals.”

“Both the SynFini and Centaur Chemist platforms have demonstrated ability to overcome key drug discovery challenges,” said Dr. Nathan Collins, chief strategy officer of SRI’s Biosciences Division and head of the SynFini program. “We believe there is tremendous potential to further accelerate the oncology drug-discovery process by combining these novel and proven technologies.”

The end-to-end SynFini platform from SRI was developed to bring new drugs to the clinic more quickly and affordably by accelerating chemical discovery and development. The SynFini closed-loop system includes three three components that work seamlessly together: a software platform (SynRoute), a reaction screening platform (SynJet) and a multi-step flow chemistry automation and development platform (AutoSyn).

Swindells noted that Exscientia is the first company to successfully apply AI technologies to design small-molecule compounds that have reached the clinic. The molecules generated by Exscientia’s Centaur Chemist platform are optimized to satisfy multiple pharmacology criteria required to enter compounds into the clinic and to achieve these goals in a rapid time scale. By using Centaur Chemist, researchers can transform drug discovery into a formalized set of moves while also enabling the system to learn strategy from human experts.

“We are optimistic about the commercial potential of bringing together the automation of both compound design and synthesis,” says Mark Swindells, chief commercial officer at Exscientia, about a collaboration with SRI International. “Drug discovery is one of the few industries remaining where key workflows are still largely human tasks. We want to automate these tasks where possible, so that we can free up the creative time of human researchers to concentrate on delivering the best overall discovery strategy.”

For better data quality, rely on the MultiFlo FX Multi-Mode Dispenser.

For more information, visit www.DDN-News.com
EXPLORE drugs such as progesterone, PB28, PD-144418 and hydroxychloroquine; the antipsychotic drugs haloperidol and cloperazone; strametine, an antiinflammatory and anti-anxiety drug; and the antihistamines clemastine and clemastine. The research team made a point to note that these drugs should be prescribed or taken to treat COVID-19 and evaluated in human clinical trials. “While these are early data, we have a high degree of confidence in the results, since similar observations on the antiviral activity of these drugs arose from work done independently at both Mount Sinai and Institut Pasteur. Research at this speed and magnitude could only have been accomplished through a collaborative effort from across the globe.”

**“While a large amount of COVID-19 therapeutic development research focuses on the antivirals and vaccines, we’ve taken a different approach, targeting the human counterparts and vulnerabilities required for viral infection in a human cell.”**

**Dr. Nevan Krogan of UC San Francisco**

were tested in SARS-CoV-2-infected cells, as were another 28 compounds proven to act upon two previously identified targets. Two particular types of drugs—protein translation inhibitors and drugs that modulate proteins known as Sigma1 and Sigma2—showed promise in reducing viral infectivity. Drugs such as zabotatin and ternatin-4/plitidepsin fall into the first category, and both are indicated for cancer treatment; zabotatin is being evaluated as a cancer therapeutic, and ternatin-4/plitidepsin has FDA approval to treat multiple myeloma. As for modulators of Sigma1/Sigma2, their work led them to several scientists at multiple institutions, each bringing unique but complementary skill sets towards a common research goal,” said Dr. Adolfo García-Sastre, professor in the Department of Microbiology and director of the Global Health and Emerging Pathogens Institute at Icahn School of Medicine at Mount Sinai.

García-Sastre and Dr. Marco Vignuzzi, principal investigator in the Viral Populations Unit at Institut Pasteur, led the virus-logical studies. In addition to identifying potential drugs for future use, this study also touched upon a potential answer for hydroxychloroquine’s adverse cardiac side effects in some studies. While the drug was found to target the Sigma1 and Sigma2 receptors, it was also revealed to bind to hERG, a protein that plays a pivotal role in regulating electrical activity in the heart.

Along those lines, their research led them to earmark another drug for further study—not as a helper, but as a hindrance. Dextromethorphan, a cough suppressant, was found to boost SARS-CoV-2 viral infection in the lab. Of the proteins identified as targets for SARS-CoV-2 infection, several were “implanted in innate immune signaling” which could help explain the erratic immune system responses and cytokine storms often seen in patients with COVID-19.

“We believe there is great potential in systematically exploring the host dependencies of the SARS-CoV-2 virus to identify other host proteins already targeted with existing drugs. Therapies targeting the host-virus interface, where mutation-al resistance is arguably less likely, could potentially present durable, broad-spectrum treatment modalities,” the authors argued in their paper. They added that they have also mapped host-pathogen interfaces in other viruses as well, such as Ebola, Dengue, Zika, herpesvirus, hepatitis C, tuberculosis, chlamydia, enteroviruses, HIV, HPV and West Nile fever.

“Excitingly, we have uncovered both shared and unique mechanisms in which these pathogens co-opt the host machinery during the course of infection. Although host-directed therapy is often not explored for combatting pathogenic infections, it would be interesting to use this information to identify host factors that could serve as targets that would harbor pan-pathogenic activity so that when the next viral outbreak arrives, we are ready,” said Dr. Jennifer C. Petter, founder and chief scientific officer of Arrakis. “This agreement with Roche underscores the value inherent in our rSM platform and will enable us to continue to develop drugs for infectious diseases.”

**ARRAKIS**

**Continued from Page 8**

ARRAKIS is developing an internal pipeline of rSMs to establish a new paradigm for small-molecule drug discovery. As part of its collaboration with Roche, Arrakis is taking a broad approach, targeting multiple mechanisms across the lifecycle of RNA to establish a new paradigm for small-molecule drug discovery. **“The collaboration will increase the number of new treatments for patients arising from our proprietary rSM discovery platform. In addition to the Roche collaboration, we are further building our capabilities and advancing our wholly owned rSM programs for diseases unadressed by today’s medicines.”**

**Dr. Michael Gilman, CEO of Arrakis**

of RNA targets, locate druggable pockets, identify drug-like hits, and conduct medici-nal chemistry programs to discover a new class of RNA-targeted medicines optimized for potency, selectivity and safety,” said Dr. Jennifer C. Petter, founder and chief scientific officer of Arrakis. “This agreement with Roche underscores the value inherent in our rSM platform and will enable us to continue to make leading discoveries and further scientific contributions in the field.”

Arrakis is taking a broad approach, target-ing multiple mechanisms across the lifecycle of RNA to establish a new paradigm for small-molecule drug discovery. The company’s dis-covery platform integrates leading-edge RNA bioinformatic and structural tools, curated chemical libraries, RNA-specific assays and RNA-guided medicinal chemistry. In addi-tion to collaborating with partners, Arrakis is developing an internal pipeline of rSMs to treat a range of serious illnesses, including cancer and other diseases where strongly validated targets and drivers of disease have been identified but have proven challenging with other drug approaches and modalities. 

EDITCONNECT: E062002

EDITCONNECT: E062006

For more information, visit www.DDN-News.com
Over time, the complexities of drug development, and was supported in the early years of the emergence of SARS, the SARS pandemic began in 2002 and was brought under control in July of 2003 as a result of isolation and screening of travelers suspected of having the virus, Akin explains. “Patients were treated similarly to how we’re treating COVID-19, with ventilators and antibiotics to treat pneumonia related to the illness. For some patients, antiviral medications and high doses of steroids to reduce inflammation in the lungs were used.”

“We are focusing our current efforts on testing VIR-2703 for COVID-19,” he continues. “However, based on the results of our initial testing, we predict there is a possibility it could be effective against other SARS genomes as well.”

The VIR-2703 program “began early this year in response to the emerging outbreak in China,” Akin tells DDN. “At the time, while we and others in the field acknowledged the possibility of a serious global impact of the new coronavirus outbreak, we did not foresee the kind of pandemic and global health crisis we are experiencing today.”

As China was shutting down its economy and ordering residents to quarantine at home, Akin says, the company began synthesizing over 350 small interfering RNAs (siRNAs), targeting highly conserved regions of the SARS-CoV-2 genome, which were then analyzed bioinformatically and assessed with in-vitro potency assays, Akin says. These efforts ultimately led to VIR-2703. “In early testing, VIR-2703 has predicted reactivity against greater than 99.9 percent of the more than 4,300 SARS-CoV-2 genomes currently available in public databases that meet analysis requirements, and is also predicted to have reactivity toward the SARS-CoV genome from the 2003 SARS outbreak, according to Akin. With this development candidate selection, Vir and Alnylam will work closely together to generate the data required to enable rapid commencement of clinical studies.

“VIR-2703, as an inhaled SARS-CoV-2-targeting siRNA, may have utility for prevention or for treatment. It leverages Alnylam’s latest advances in lung delivery of siRNAs, and may have applicability to other coronaviruses as well. VIR-2703 is the first development candidate selected in the company’s expanded collaboration with Alnylam, which covers up to four RNAi potential therapeutics for COVID-19.”

“We are encouraged by the results we have obtained to date, we have not yet started human clinical trials, so it is too soon to tell if VIR-2703 will be effective against COVID-19 in people,” Akin says.

And looking toward the wider pharma community doing similar work, he adds, “We are hopeful that the bright scientists working on this throughout the industry will win the battle against COVID-19.”

George Scangos, CEO of Vir, says with this development candidate now in hand, “Our ultimate goal would be to provide rapid worldwide access, if approved, to an effective therapeutic to combat COVID-19.”

**Critical Antibodies & Reagents**

Rockland has a long history of providing critical antibodies and related tools as a qualified raw material manufacturer based in Limerick, Pennsylvania. We hold critical stock on hand, scale up and supplement production activities, deliver services customized to your specific needs, and leverage our global network to source and deliver products critical to your important work. During these challenging times, let’s work together to advance science.

Contact us at sales@rockland-inc.com or visit our website to learn more!
Editor’s Focus: Cancer, COVID and change

BY JEFFREY BOULEY

O UR REGULAR column- nist and guest col- umnist have plenty to say this month, so I’ll keep it short and sweet and just let you know what’s going on with this issue—and future publications—and more.

As is traditional, the June issue is pretty heavily cancer-focused, and we have oncology-related content not just in miscellaneous news sto- ries throughout the issue, but also in the form of a Special Report begin- ning on page 17 and a Focus Feature starting on page 27.

Not only that, but that other C-word, COVID, is also prominent—first in Peter Kissinger’s column below, but also in several stories throughout the various news sections, in particular our “Research & Development” section starting on page 12.

Heck, even we have a story titled “COVID and cancer” in this issue. The article on News page 38 if you want to get both topics in one dose.

Certainly, it’s no exaggeration to say that COVID-19 has turned everything upside down. We even launched an e-newsletter devoted to the topic in April. Our second one went out in May, and we’ve got another planned for June. Right now it’s a monthly thing, but that could change—upward or downward—as the situation on the field changes. And even once the novel coronavirus is (hopefully) relegated to minor-league status, we shall look backward to practice at least one therapeutic area-focused e- newsletter each month.

Not to mention that we’re reti- ring the DDNews Online bi-weekly e-newsletter for a new weekly one titled DDNews Online Weekly Roundup, which begins this month and will focus only on very recent news, whereas the old e-newsletter also featured highlights from the current issue of the magazine. That latter duty will be filled by another new e-newsletter launching in July called DDNews Monthly Insider.

Also, as I’m writing this, we are on the verge of conducting our very first webinar, focused on COVID-19, with Peter Kissinger and me discussing the topic on antibody therapeu- tics in cancer.

Yeah, there’s a reason the head-line of this column includes the word “change.” And there are more exciting changes and offer- ings coming up from us in the DDN family, so stay tuned.

TESTING, TESTING, TESTING...1,2,3,4

BY PETER T. KISSINGER

O VER THE LAST couple of months, we’ve heard more about testing than in my five decades in test- ing. The babble has been repetitive enough to remind me of micro- phone checks at conferences where I was an invited speaker. March was “mask and ventilator” month, April grabbed testing, and May has run strong with testing, drugs and vaccines.

As a professional tester, it is flat- tering to finally be recognized. On the other hand, the ambiguities of diagnostic testing are evidently not widely appreciated. Let’s con- sider some details with respect to COVID-19. First, there are three quality attributes for all test devices: all can- ners should have at home: a blood pressure monitor, a thermom- eter and a finger pulse oximeter. Together, they cost less than one dollar and a finger pulse oximeter.

Besides, those known to have been exposed to an infected person, and those known to have been exposed to a confirmed person should have at home: a blood pressure monitor, a thermometer and a finger pulse oximeter. Together, they cost less than one dollar and a finger pulse oximeter.

Are the tests valid?

As a professional tester, it is flat- tering to finally be recognized. On the other hand, the ambiguities of diagnostic testing are evidently not widely appreciated. Let’s consider some details with respect to COVID-19. First, there are three quality attributes for all test devices: all can- ners should have at home: a blood pressure monitor, a thermo- meter and a finger pulse oximeter. Together, they cost less than one dollar and a finger pulse oximeter.

Besides, those known to have been exposed to an infected person, and those known to have been exposed to a confirmed person should have at home: a blood pressure monitor, a thermometer and a finger pulse oximeter. Together, they cost less than one dollar and a finger pulse oximeter.

Peter Kissinger, Purdue University Professor Emeritus
I intended to treat a serious or life-threatening condition and review time of promising new therapies. This suggests biopharma organizations’ impact on global health is not only thriving but also delivering measurable therapeutic and commercial benefits.

A new way to look at the state of pharma innovation

Based on an analysis of the new drugs approved by the FDA, small molecules continue to be an important drug modality, as they continue to represent the majority of the approved new therapeutic drugs (not including diagnostic imaging agents) in 2019. Recent studies have shown that the exploration of chemical space is proceeding along two tracks: the re-use of known structural cores (resulting in molecules with some structural similarity to previous ones) and the creation of new structural cores (producing structurally novel molecules). A majority of the recently approved small-molecule drugs followed the latter track, as they included at least one structurally novel small molecular entity (NME) whose structural core was not used in any previously FDA-approved drugs.

Balancing innovation with efficiency is a longstanding challenge in drug discovery. A typical drug discovery project only has the budget and time to synthesize and assay fewer than 10,000 molecules. With the number of potentially synthetizable organic molecules estimated to be 10^6 (for those below 1000 Da.), efficiency in exploring the vastness of chemical space is beyond the reach of current experimental approaches. However, exploring such a limited percentage of potential molecules obviously results in missed opportunities when seeking to identify the most promising novel drug-like molecules.

A structurally novel drug candidate can be much more impactful to a drug discovery project than the identification of many close analogues of a known molecule. As proof of that point, we can look to drugs designated as breakthrough therapies. Utilizing the breakthrough therapy designation (BTD) as a proxy of a drug’s potential impact on public health, analysis shows that structurally novel small-molecule drugs are more likely to be the source of promising new therapies. This suggests biopharma organizations’ impact on global health would benefit significantly from adopting technology-driven approaches that support more efficient and far-reaching exploration of deep chemical space.

BTD: The real-world impact of structural novelty

Breakthrough Therapy Designation was introduced in 2012 to heighten the development and review time of promising new therapies intended to treat a serious or life-threatening disease for which there is unmet medical need, and for which there is evidence to demonstrate a potential substantial improvement on a clinically significant endpoint compared with other available therapies. Once a drug is designated as a breakthrough therapy, the FDA will expedite the development and review process in order to reduce the drug’s time to market. Receiving BTD status is undoubtedly challenging, as evidenced by the 60 percent rejection rate for BTD applicants; however, the designation brings with it both public health and commercial benefits.

Studies have found that in addition to review periods being shortened by around three months, BTD drugs will spend two to three years less in pre-market development compared with non-BTD drugs. Furthermore, receiving this designation provides some credibility to the clinical promise of a given product and, as a result, adds significant value to a company. In fact, our analysis of publicly announced BTD grants found that the stock of publicly traded companies without any marketed products rose by an average of 6 percent (in excess of market returns) the day after BTD was announced.

Between 2013 and 2019, 73 (26 percent) of the 276 new therapeutic drugs approved by the FDA’s Center for Drug Evaluation and Research were granted breakthrough drug status. Almost 60 percent of these were small-molecule drugs, over 80 percent of which included at least one structurally novel NME. However, this does not tell the complete story. Taking a deeper look, we find structurally novel, small-molecule drugs are 2.5 times more likely to be designated as breakthrough therapies—30 percent of the structurally novel small-molecule drugs achieve breakthrough status, compared to only 12 percent of the non-structurally novel small-molecule drugs. Machine learning is one of the primary in silico methods that many biopharma organizations have attempted to deploy over the last several years. Machine learning algorithms are only as good as the training data sets on which they are based. Therefore, more and better training data is an obvious way to improve an algorithm’s prediction accuracy. Molecular descriptors also play an essential role in the performance of machine learning algorithms in chemistry-related applications. Molecular fingerprints are a common way to encode the structure of a molecule in a form that is amenable for machine learning. In a series of validation tests using common predictive machine learning algorithms, the accuracy achieved with a new molecular fingerprint developed by CAS scientists outperformed the commonly used Morgan fingerprint by up to 4 percent. These fingerprints are being used by CAS in drug discovery consulting projects that incorporate machine learning to predict properties of drug-like molecules. Improved property predictions reduce the number of molecules that must be synthesized for testing. As a result, resources can be focused on synthesizing and assaying candidate drugs with more optimal drug-like properties. The resulting more structurally diverse candidate pools provide a better selection of molecules, increasing the odds of finding more effective drug candidates.

As these advancements help drug hunters push the boundaries to find structurally novel small-molecule drugs, it will empower them to more efficiently seek out and assess the highest-potential opportunities from a wider set of structural possibilities. Based on the aforementioned odds, the resulting structurally novel small-molecule drugs are more likely to be the source of promising new breakthrough therapies. The result will hopefully be a virtuous cycle that will incentivize others to venture deeper into chemical space, causing a more rapid advance of public health and driving incremental growth in innovation.

REFERENCES

1. Roque Change in the School of Organic Chemistry As Soon in the CAS Registry https://pubs.acs.org/doi/10.1021/acs.joc.9b01211

2. Impact of Breakthrough Therapy Designation on Cancer Drug Development https://www.nature.com/articles/jnci.2016.19

3. The FDA’s Role in the Development and Approval of Breakthrough Drugs and its Timing for Novel Therapeutics, 2012-2016 https://panasymposium.com/journals/jama/ fullarticle/286/1898S


COMMENTARY: ACCELERATING THE PACE OF PHARMA INNOVATION AT A MOLECULAR LEVEL

By Todd Wills, Managing Director of CAS

N 2019, the U.S. Food and Drug Administration (FDA) approved just 42 new drugs. This drop-off, compared to 2018 when 59 new drugs were approved, unsurprisingly led some pharma industry analysts to rekindle recent concerns over an innovation crisis.

However, when one looks beyond strictly the number of approvals more deeply into the drugs themselves, there is actually significant evidence to the contrary. In fact, it appears that from a chemical structure perspective, innovation in drug discovery is not only thriving but also delivering measurable therapeutic and commercial benefits.

A new way to look at the state of pharma innovation

Based on an analysis of the new drugs approved by the FDA, small molecules continue to be an important drug modality, as they continue to represent the majority of the approved new therapeutic drugs (not including diagnostic imaging agents) in 2019. Recent studies have shown that the exploration of chemical space is proceeding along two tracks: the re-use of known structural cores (resulting in molecules with some structural similarity to previous ones) and the creation of new structural cores (producing structurally novel molecules). A majority of the recently approved small-molecule drugs followed the latter track, as they included at least one structurally novel small molecular entity (NME) whose structural core was not used in any previously FDA-approved drugs.

Balancing innovation with efficiency is a longstanding challenge in drug discovery. A typical drug discovery project only has the budget and time to synthesize and assay fewer than 10,000 molecules. With the number of potentially synthetizable organic molecules estimated to be 10^6 (for those below 1000 Da.), efficiency in exploring the vastness of chemical space is beyond the reach of current experimental approaches. However, exploring such a limited percentage of potential molecules obviously results in missed opportunities when seeking to identify the most promising novel drug-like molecules.

A structurally novel drug candidate can be much more impactful to a drug discovery project than the identification of many close analogues of a known molecule. As proof of that point, we can look to drugs designated as breakthrough therapies. Utilizing the breakthrough therapy designation (BTD) as a proxy of a drug’s potential impact on public health, analysis shows that structurally novel small-molecule drugs are more likely to be the source of promising new therapies. This suggests biopharma organizations’ impact on global health would benefit significantly from adopting technology-driven approaches that support more efficient and far-reaching exploration of deep chemical space.

BTD: The real-world impact of structural novelty

Breakthrough Therapy Designation was introduced in 2012 to heighten the development and review time of promising new therapies intended to treat a serious or life-threatening disease for which there is unmet medical need, and for which there is evidence to demonstrate a potential substantial improvement on a clinically significant endpoint compared with other available therapies. Once a drug is designated as a breakthrough therapy, the FDA will expedite the development and review process in order to reduce the drug’s time to market. Receiving BTD status is undoubtedly challenging, as evidenced by the 60 percent rejection rate for BTD applicants; however, the designation brings with it both public health and commercial benefits.

Studies have found that in addition to review periods being shortened by around three months, BTD drugs will spend two to three years less in pre-market development compared with non-BTD drugs. Furthermore, receiving this designation provides some credibility to the clinical promise of a given product and, as a result, adds significant value to a company. In fact, our analysis of publicly announced BTD grants found that the stock of publicly traded companies without any marketed products rose by an average of 6 percent (in excess of market returns) the day after BTD was announced.

Between 2013 and 2019, 73 (26 percent) of the 276 new therapeutic drugs approved by the FDA’s Center for Drug Evaluation and Research were granted breakthrough drug status. Almost 60 percent of these were small-molecule drugs, over 80 percent of which included at least one structurally novel NME. However, this does not tell the complete story. Taking a deeper look, we find structurally novel, small-molecule drugs are 2.5 times more likely to be designated as breakthrough therapies—30 percent of the structurally novel small-molecule drugs achieve breakthrough status, compared to only 12 percent of the non-structurally novel small-molecule drugs. Machine learning is one of the primary in silico methods that many biopharma organizations have attempted to deploy over the last several years. Machine learning algorithms are only as good as the training data sets on which they are based. Therefore, more and better training data is an obvious way to improve an algorithm’s prediction accuracy. Molecular descriptors also play an essential role in the performance of machine learning algorithms in chemistry-related applications. Molecular fingerprints are a common way to encode the structure of a molecule in a form that is amenable for machine learning. In a series of validation tests using common predictive machine learning algorithms, the accuracy achieved with a new molecular fingerprint developed by CAS scientists outperformed the commonly used Morgan fingerprint by up to 4 percent. These fingerprints are being used by CAS in drug discovery consulting projects that incorporate machine learning to predict properties of drug-like molecules. Improved property predictions reduce the number of molecules that must be synthesized for testing. As a result, resources can be focused on synthesizing and assaying candidate drugs with more optimal drug-like properties. The resulting more structurally diverse candidate pools provide a better selection of molecules, increasing the odds of finding more effective drug candidates.

As these advancements help drug hunters push the boundaries to find structurally novel small-molecule drugs, it will empower them to more efficiently seek out and assess the highest-potential opportunities from a wider set of structural possibilities. Based on the aforementioned odds, the resulting structurally novel small-molecule drugs are more likely to be the source of promising new breakthrough therapies. The result will hopefully be a virtuous cycle that will incentivize others to venture deeper into chemical space, causing a more rapid advance of public health and driving incremental growth in innovation.
BRIEFS

MEANINGFUL BIOMARKERS

Precision medicine analyses show potential for Alzheimer’s drug
BY ILENE SCHNEIDER

NEW YORK—Alzheimer’s disease (AD) is a neurodegenerative process that causes memory loss and other cognitive impairments, gradually destroying an individual’s intellect and personality. A progressive, multi-factorial disease, it is the most common cause of primary neurodegenerative dementias. About 5.7 million people in the U.S. have Alzheimer’s disease, and about 50 million are stricken worldwide. The current annual cost of dementia is estimated at $1 trillion, a figure expected to double by 2030. There are no treatments for it at this time.

The April 2020 issue of Alzheimer’s & Dementia: Translational Research & Clinical Interventions reported on a drug under development by Anavex Life Sciences, a clinical-stage biopharmaceutical company. Anavex seeks to create specific therapies developing differentiated therapeutics for the treatment of neurodegenerative and neurodevelopmental diseases such as Alzheimer’s disease, Parkinson’s disease, Rett syndrome and other central nervous system (CNS) diseases. The article is titled “A precision medicine framework using Artificial Intelligence for the identification and confirmation of genomic biomarkers of response to an Alzheimer’s disease therapy: Analysis of the Blarcamesine (ANAVEX2-73) Phase 2a clinical study.”

Building a Biobank

Biogen, Broad Institute and Partners HealthCare create consortium for COVID-19 efforts
BY MEL J. YEATES

CAMBRIDGE, Mass.—Biogen Inc., the Broad Institute of MIT and Harvard, and Partners HealthCare recently established a consortium for the purpose of building and sharing a COVID-19 biobank. The biobank, which will consist of a large collection of de-identified biological and medical data, will help scientists to advance their knowledge of the virus and search for potential vaccines and treatments.

“The COVID-19 pandemic has had a very direct, very personal impact on our Biogen community,” says Dr. Maha Byloe, AUM launches Knockdown Coronavirus

RNA could be the kryptonite to defeat COVID-19
BY LORI LESKO

PHILADELPHIA—With the coronavirus pandemic disrupting life as we know it, preclinical-stage biotech AUM LifeTech Inc. and genetic screening startup AUM BioTech LLC have had enough and are ready to fight the deadly virus facing the world today. The companies have joined hands and resources to kick off Knockdown Coronavirus, a research program aimed at developing a treatment for COVID-19.

Under this initiative, the two companies are offering self-delivering RNA silencing research products, powered by FANA ASO technology, to the global coronavirus research community to facilitate research and fast-track therapeutic development.

AUM LifeTech is currently working with collaborators toward the goal of developing a therapy for COVID-19, while AUM BioTech’s next-generation gene-silencing research tools have the capability to selectively knockdown the virus’ RNA. Further, AUM BioTech’s RNA-targeting technology can be used to perform high-throughput genetic screening to identify the function of viral and host genes, and help identify new targets for COVID-19 therapy development.

“We are very excited to launch this program and serve the global scientific community, which is working tirelessly to find a cure for COVID-19 in these unique and challenging times,” says Veenu Aishwarya, founder and CEO of AUM LifeTech and AUM BioTech. “RNA-targeting technology works by silencing (knocking down) the RNA that plays a crucial role, causing a loss of function, thus inhibiting viral replication and transmission.”

“We are very proud to offer our RNA-silencing platform to better understand the biology of SARS-CoV-2 and its interaction with the host. Our goal is to provide our expertise and resources to facilitate COVID-19 research with a hope to develop a potential antiviral therapy for COVID-19, using our self-delivering FANA ASO technology,” he adds. “Additionally, we are actively seeking new alliances, and invite the scientific community to partner with us to knockdown coronavirus and defeat COVID-19.”

Aishwarya notes that SARS-CoV-2 “is an RNA virus,” which means that “Simply speaking, using our RNA-targeting approach we can shut down critical components of the virus.”
and again at more than three years (148 weeks). Researchers believe the study provides a template for the use of big data in precision medicine studies of new therapies for neurological disorders.

The article explained that “Formal concept analysis (FCA) is less affected by population size than other statistical analysis platforms. In this study, FCA, integrated in Knowledge Extraction and Management (KEM) software (v.9.6.2), was used to identify and rank phenotypic and genotypic biomarkers. No link was assumed in these analyses of biomarkers and therapeutic responses, enabling a hypothesis-free, data-driven tabulation of all relational effects between potential biomarkers and therapeutic responses in patients with AD.”

According to Dr. Harald Hampel, founding president of the Alzheimer Precision Medicine Initiative (APMI) and lead author of the paper, “This study highlights the relevance of phenotypic and genotypic precision medicine analyses of whole-exome sequencing and gene expression data in drug development [particularly] to identify patients’ genetic variants and gene expression changes that may predict increased chances of success of Alzheimer’s disease treatments.”

Dr. Harald Hampel of the Alzheimer Precision Medicine Initiative
Michael J. Fox Foundation for Parkinson’s Research grant to Anavex. There will now be a Phase 2b/3 AD study to locate patients with Parkinson’s disease, dementia or Rett syndrome who will benefit from this drug.

Another drug being advanced by the company is ANAVEX3-71, which targets Sigma1 and muscarinic receptors. The compound is a preclinical candidate demonstrating disease-modifying activity against the major hallmarks of Alzheimer’s disease in transgenic (3xTg-AD) mice, including cognitive deficits, amyloid and tau pathology. In preclinical trials, ANAVEX3-71 has shown beneficial effects on mitochondrial dysfunction and neuroinflammation.

“We believe that the analysis platform described in this work opens the possibility of using big data-driven, unbiased, genome-wide patient selection marker identification early on in the drug development process of CNS diseases,” says Dr. Christopher U. Missling, president and CEO of Anavex.

As a preclinical candidate demonstrating disease-modifying activity against the major hallmarks of Alzheimer’s disease in transgenic (3xTg-AD) mice, including cognitive deficits, amyloid and tau pathology. In preclinical trials, ANAVEX3-71 has shown beneficial effects on mitochondrial dysfunction and neuroinflammation. We believe that the analysis platform described in this work opens the possibility of using big data-driven, unbiased, genome-wide patient selection marker identification early on in the drug development process of CNS diseases,” says Dr. Christopher U. Missling, president and CEO of Anavex.

This study highlights the relevance of phenotypic and genotypic precision medicine analyses of whole-exome sequencing and gene expression data in drug development [particularly] to identify patients’ genetic variants and gene expression changes that may predict increased chances of success of Alzheimer’s disease treatments.

Dr. Harald Hampel of the Alzheimer Precision Medicine Initiative
Michael J. Fox Foundation for Parkinson’s Research grant to Anavex. There will now be a Phase 2b/3 AD study to locate patients with Parkinson’s disease, dementia or Rett syndrome who will benefit from this drug.

Another drug being advanced by the company is ANAVEX3-71, which targets Sigma1 and muscarinic receptors. The compound is a preclinical candidate demonstrating disease-modifying activity against the major hallmarks of Alzheimer’s disease in transgenic (3xTg-AD) mice, including cognitive deficits, amyloid and tau pathology. In preclinical trials, ANAVEX3-71 has shown beneficial effects on mitochondrial dysfunction and neuroinflammation.

“We believe that the analysis platform described in this work opens the possibility of using big data-driven, unbiased, genome-wide patient selection marker identification early on in the drug development process of CNS diseases, including Alzheimer’s disease, which is currently applied more routinely in the field of oncology,” added Dr. Christopher U. Missling, president and CEO of Anavex.

“Findings from this study were the basis for the testing of potential patient selection markers in our ongoing Phase 2b/3 Alzheimer’s disease (AD) study, as well as the Parkinson’s disease dementia and Rett syndrome studies with ANAVEX7-13 (bicalutamide).”

According to the article, the FCA platform “opens the possibility of using data-driven unbiased biomarker identification early in the drug development process. The white box and systematic approach of FCA is ideal for the analysis of early data, leading to the identification of patient selection biomarkers that can assist in the design of more effective subsequent clinical trials.”

The study was funded by a


date blood samples will be generated at the Broad Institute and de-identified. The biobank will provide a unique, anonymous medical and biological dataset.

“The biobank will also store frozen samples, which may inform future research with appropriate patient consent,” Radhakrishnan points out.

Biogen will have the same level of access to the biobank as any other researchers around the world. The company won’t have access to identifiable information, or know which employees and close contacts volunteered to participate.

“Patients who have volunteered to donate data … play a crucial role in the global effort to overcome COVID-19. Through a shared biobank, researchers will be able to identify new patterns and drastically expand our knowledge of a disease,” said Eric S. Lander, president and founding director of the Broad Institute. “We are enormously grateful to the Biogen employees, their family members and other close contacts who have volunteered to take part in this essential effort.”

“We’re grateful to these individuals for their willingness to participate, and hope that by sharing their data, researchers everywhere will be able to make new discoveries that point the way toward effective treatments,” concluded Hung.

This study highlights the relevance of phenotypic and genotypic precision medicine analyses of whole-exome sequencing and gene expression data in drug development [particularly] to identify patients’ genetic variants and gene expression changes that may predict increased chances of success of Alzheimer’s disease treatments.

Dr. Harald Hampel of the Alzheimer Precision Medicine Initiative
Michael J. Fox Foundation for Parkinson’s Research grant to Anavex. There will now be a Phase 2b/3 AD study to locate patients with Parkinson’s disease, dementia or Rett syndrome who will benefit from this drug.

Another drug being advanced by the company is ANAVEX3-71, which targets Sigma1 and muscarinic receptors. The compound is a preclinical candidate demonstrating disease-modifying activity against the major hallmarks of Alzheimer’s disease in transgenic (3xTg-AD) mice, including cognitive deficits, amyloid and tau pathology. In preclinical trials, ANAVEX3-71 has shown beneficial effects on mitochondrial dysfunction and neuroinflammation.

“We believe that the analysis platform described in this work opens the possibility of using big data-driven, unbiased, genome-wide patient selection marker identification early on in the drug development process of CNS diseases,” says Dr. Christopher U. Missling, president and CEO of Anavex.

This study highlights the relevance of phenotypic and genotypic precision medicine analyses of whole-exome sequencing and gene expression data in drug development [particularly] to identify patients’ genetic variants and gene expression changes that may predict increased chances of success of Alzheimer’s disease treatments.

Dr. Harald Hampel of the Alzheimer Precision Medicine Initiative
Michael J. Fox Foundation for Parkinson’s Research grant to Anavex. There will now be a Phase 2b/3 AD study to locate patients with Parkinson’s disease, dementia or Rett syndrome who will benefit from this drug.

Another drug being advanced by the company is ANAVEX3-71, which targets Sigma1 and muscarinic receptors. The compound is a preclinical candidate demonstrating disease-modifying activity against the major hallmarks of Alzheimer’s disease in transgenic (3xTg-AD) mice, including cognitive deficits, amyloid and tau pathology. In preclinical trials, ANAVEX3-71 has shown beneficial effects on mitochondrial dysfunction and neuroinflammation.

“We believe that the analysis platform described in this work opens the possibility of using big data-driven, unbiased, genome-wide patient selection marker identification early on in the drug development process of CNS diseases, including Alzheimer’s disease, which is currently applied more routinely in the field of oncology,” added Dr. Christopher U. Missling, president and CEO of Anavex.

“Findings from this study were the basis for the testing of potential patient selection markers in our ongoing Phase 2b/3 Alzheimer’s disease (AD) study, as well as the Parkinson’s disease dementia and Rett syndrome studies with ANAVEX7-13 (bicalutamide).”

According to the article, the FCA platform “opens the possibility of using data-driven unbiased biomarker identification early in the drug development process. The white box and systematic approach of FCA is ideal for the analysis of early data, leading to the identification of patient selection biomarkers that can assist in the design of more effective subsequent clinical trials.”

The study was funded by a

This study highlights the relevance of phenotypic and genotypic precision medicine analyses of whole-exome sequencing and gene expression data in drug development [particularly] to identify patients’ genetic variants and gene expression changes that may predict increased chances of success of Alzheimer's disease treatments.

Dr. Harald Hampel of the Alzheimer Precision Medicine Initiative
Michael J. Fox Foundation for Parkinson’s Research grant to Anavex. There will now be a Phase 2b/3 AD study to locate patients with Parkinson’s disease, dementia or Rett syndrome who will benefit from this drug.

Another drug being advanced by the company is ANAVEX3-71, which targets Sigma1 and muscarinic receptors. The compound is a preclinical candidate demonstrating disease-modifying activity against the major hallmarks of Alzheimer’s disease in transgenic (3xTg-AD) mice, including cognitive deficits, amyloid and tau pathology. In preclinical trials, ANAVEX3-71 has shown beneficial effects on mitochondrial dysfunction and neuroinflammation.

“We believe that the analysis platform described in this work opens the possibility of using big data-driven, unbiased, genome-wide patient selection marker identification early on in the drug development process of CNS diseases, including Alzheimer’s disease, which is currently applied more routinely in the field of oncology,” added Dr. Christopher U. Missling, president and CEO of Anavex.

“Findings from this study were the basis for the testing of potential patient selection markers in our ongoing Phase 2b/3 Alzheimer’s disease (AD) study, as well as the Parkinson’s disease dementia and Rett syndrome studies with ANAVEX7-13 (bicalutamide).”

According to the article, the FCA platform “opens the possibility of using data-driven unbiased biomarker identification early in the drug development process. The white box and systematic approach of FCA is ideal for the analysis of early data, leading to the identification of patient selection biomarkers that can assist in the design of more effective subsequent clinical trials.”

The study was funded by a
Suppression of immune system may be key to reducing COVID-19 severity

BY DDN STAFF

LOS ANGELES—A new study coming out of the University of Southern California (USC) suggests that temporarily suppressing the body’s immune system during the early stages of COVID-19 could help a patient avoid severe symptoms, because the timing of the immune response to the disease may increase its severity.

The research, recently published online under the title “Mathematical modeling of interactions between innate and adaptive immune responses in COVID-19—and implications for viral pathogenesis” in the Journal of Medical Virology, shows that an interaction between two innate immune responses may be causing the immune system to go into overdrive in some patients.

As a news release from USC notes of the research, the body’s first line of defense—the innate immune response—starts right after an infection, “like an infancy going after a foreign invader, killing the virus and any cells damaged by it.” The second line of defense— the adaptive immune response—kicks in days later if any viruses remain, “employing what it has learned about the virus to mobilize a variety of special forces such as T cells and B cells.”

Using the “target cell-limited model,” a common mathematical model developed to understand the dynamics of viral infections, the researchers examined how the two immune responses work in COVID-19 patients compared to patients who have the flu.

The flu is a fast-moving infection that attacks certain target cells on the surface of the upper respiratory system and kills almost all of the target cells within two to three days. The death of these cells deprives the virus of more targets to infect and allows the innate immune response time to clear the body of almost all of the virus before the adaptive system comes into play.

But COVID-19, which targets surface cells throughout the respiratory system (including in the lungs), has an average incubation of six days and a much slower disease progression.

Mathematical modeling suggests that the adaptive immune response may kick in before the target cells are depleted, slowing down the infection and interfering with the innate immune response’s ability to kill off most of the virus quickly.

“The danger is, as the infection keeps going on, it will mobilize the whole of the adaptive immune response with its multiple layers,” explained Weiming Yuan, an associate professor in the Department of Molecular Microbiology and Immunology at the Keck School of Medicine of USC and co-responding author of the study. “This longer duration of viral activity may lead to an overreaction of the immune system called a cytokine storm, which kills healthy cells, causing tissue damage.”

The interaction of the innate and the adaptive immune responses might also explain why some COVID-19 patients experience two waves of the disease, appearing to get better before eventually getting much worse.

“The interaction of the innate and the adaptive immune responses might also explain why some COVID-19 patients experience two waves of the disease, appearing to get better before eventually getting much worse. “Some COVID-19 patients may experience a resurgence of the disease after an apparent easing of symptoms,” noted Sean Du, an adjunct researcher and lead author of the study. “It’s possible that the combined effect of the adaptive and the innate immune responses may reduce the virus to a low level temporarily. However, if the virus is not completely cleared and the target cells regenerate, the virus can take hold again and reach another peak.”

The most provocative result of the research is the kind of treatment it suggests to prevent this interaction between the two immune responses.

“Based on the results of the mathematical modeling, we proposed a counterintuitive idea that a short regimen of a proper immunosuppressant drug applied early in the disease process may improve a patient’s outcome,” said Du. “With the right suppressive agent, we may be able to delay the adaptive immune response and prevent it from interfering with the innate immune response, which enables faster elimination of the virus and the infected cells.”

Small studies out of China, including a recent one of COVID-19 patients and one of SARS patients in 2003, show patients who received immunosuppressants such as corticosteroids had better results than those who did not.

The researchers said a possible next step could be to take daily measurements of viral loads and other biomarkers in COVID-19 patients, to see if the data validates the mathematical modeling. More preclinical studies, including experiments in animal models, will also be needed to prove the efficacy of an early immune-suppressing treatment.

“Simply speaking, using our RNA-targeting approach we can shut down critical components of the virus (required for its survival) and inhibit its replication and transmission.”

Veenu Aishwarya, CEO of AUM LifeTech and AUM BioTech

McGill University in Canada on another COVID-19 project using FANA ASO technology. FANA ASO technology “can be used in two ways,” Aishwarya explains. “One, as a research tool and two, as a potential therapeutic. With our RNA-targeting technology we can identify the critical genes which are needed for the survival of coronavirus. This information can help us to better understand the biology of SARS-CoV-2 and its interaction with the host (i.e. humans or other animals).”

“Once we have identified this information, we can then use the same FANA ASO technology to develop a potential RNA-targeting therapeutic for COVID-19,” he adds. “This approach can save us lot of time and resources.”

At AUM LifeTech, “we are in the very beginning stages of development,” he notes. “Our hope is that with our next-generation RNA-silencing technology, we will be able to significantly shorten this time, but we still have a long way to go and follow a data driven approach to find a potential therapy for COVID-19.”

As for the end of this pandemic, Aishwarya says, “I am an optimist. It has to be a combined effort from every member of our species. It is nice to see that people are already contributing in the best way they can. It may take some time to completely figure this one out as we prepare for the next one.”
Data recommend RECCE 327
Synthetic antibiotic shows efficacy against priority antibiotic-resistant pathogen

BY JIM CIRIGLIANO
SYDNEY—Australian drug developer Recce Pharmaceuticals has announced new data showing significant in-vivo antibiotic activity in mice treated with its lead compound RECCE 327 against Neisseria gonorrhoeae, the second most common sexually transmitted infection (STI). RECCE 327 is among a new class of synthetic antibiotics with broad-spectrum activity developed for the treatment of blood infections and sepsis derived from E. coli and S. aureus bacteria, including their drug-resistant forms.

An independent contract research organization conducted the study to assess the dose-dependency of the compound and its in-vivo antibacterial activity against N. gonorrhoeae. The study’s results, shared in May 2020, showed the model met its primary endpoint of a significant reduction in bacterial load compared to the control at multiple dosing levels, as measured seven days after dosing.

Recce is developing a new class of broad-spectrum antibiotics with activity against multiple serious and potentially life-threatening multidrug-resistant pathogens, including the potential to remain effective against drug-resistant bacteria even with repeated use. Recent animal data with lead compound RECCE 327 vs. Neisseria gonorrhoeae have been promising.

Recce is developing a new class of broad-spectrum antibiotics against multidrug-resistant pathogens, including the potential to remain effective against drug-resistant bacteria even with repeated use. According to the company, there have been no new classes of antibiotics developed in more than 30 years, and antibiotics dosing levels, as measured seven days after dosing.

Recce is developing a new class of broad-spectrum antibiotics against multidrug-resistant pathogens, including the potential to remain effective against drug-resistant bacteria even with repeated use. According to the company, there have been no new classes of antibiotics developed in more than 30 years, and antibiotics.
used to prevent and treat bacterial infections are becoming less effective due to the development of antibiotic resistance. Antibiotic resistance occurs when bacteria no longer respond to the drugs designed to kill them, and has been caused primarily by decades of overuse and misuse of antibiotics.

“The need for new antibiotics has never been greater, as bacteria have developed resistance to most currently approved antibiotics,” says James Graham, executive director of Recce Pharmaceuticals. “Traditional antibiotics operate by a ‘lock-and-key’ mechanism of action. When a bacterium mutates, or evolves, that mechanism of traditional antibiotics no longer functions because the lock has changed. The new class of broad-spectrum antibiotics for severe, life-threatening infections caused by resistant organisms will not develop resistance.”

Recce Pharmaceuticals is preparing to support its first-in-human clinical trials. Recce 327 is patented, wholly owned and manufactured in Australia. The company plans to develop the new class of broad-spectrum antibiotics for several diverse applications.

According to Graham, “Lead candidate Recce 327 has demonstrated high potency against a range of Gram-positive and Gram-negative bacteria. While we continue to expand our pipeline, we plan on advancing Recce 327 and new formulations of the drug for other serious infectious diseases. Synthetic polymer drugs have the potential to be effective against deadly superbugs beyond those that are bacterial in origin, including viruses.”

Recce 327 was recently awarded a Qualified Infectious Disease Product designation for sepsis under the German Infectious Disease Initiatives Now Act by the U.S. Food and Drug Administration, which helps to fast-track the compound through the regulatory review process and grants 10 years of marketing exclusivity post approval. Graham says Recce antibiotics are easily formulated for topical, nasal, oral or inhalation use, and this versatility will be beneficial when developing antibiotics for indications other than sepsis.

“Having completed its preclinical studies assessing Recce 327, the company expects to move into its first-in-human Phase 1 trial in the second half of 2020,” Graham reports. “The randomized, double-blind, placebo-controlled, single ascending dose study will evaluate the safety, tolerability, pharmacokinetic and pharmacodynamic properties of the pertussis toxin 327 administered by intranasal infusion. In parallel to this study, we anticipate a topical efficacy trial at a leading teaching hospital in Australia to assess RCF’s efficacy in reducing bacterial load in wounds and assisting in wound closure of skin infections and burns.”

IMMUNO

“IMP761 is the only LAG-3 agonist mAb which has been published. It took us more than 20 years to end up finding our agonist LAG-3 mAb, screening hundreds of hybridomas in a functional assay,” says Dr. Frederic Triebel, chief scientific officer and chief medical officer of Immune.

LAG-3 has to touch the right button (i.e., the right functional B-cell epitope) on the N-terminal domain of LAG-3 (i.e., the one in direct contact with its ligands, MHC class II molecules) to be able to mimic the ligand and strengthen the induced negative signaling mediated by LAG-3. So, quite difficult to find.”

“Of course, as the function of LAG-3 is known and numerous blocking LAG-3 mAbs are currently being tested in pivotal trials in immunology-oxidant validating LAG-3 as an important target in patients, the potential use of IMP761 as an LAG-3 mAb should be of course in autoimmune diseases (AID),” he states. “For more than 95 percent of AID, the root cause has been defined primarily by a break of tolerance of a few T cells by recognizing a given self-antigen (e.g., a skin protein, in the case of psoriasis) too strongly … leading to the killing of the target tissues (e.g., the skin) harboring this antigen either by the production of cytotoxic immunoglobulins or the generation of cytotoxic CD8 T cells.”

The pharmacology of indi- stable CHO cell clones which were developed have provided significantly higher product yields than the initial IMP761 product candidate than the companies had initially anticipated. These results will permit a smooth transition to the development stage. In 2019, Batavia licensed Horizon Discovery’s GS-knockout CHO expression system, CHOSOURCE. The full scale production process—incuding cell line generation, process development and manufacturing—is marketed by Batavia as ‘N’. The company has now been awarded €10,000 to the researcher/research group whose publication in neuroscience research best exemplifies data where the results do not confirm the expected outcomes or original hypotheses.

The GPDF consists of members from the academic, non-profit, government, publishing and industry sectors and aims to encourage global collaboration to address the challenge of ensuring that preclinical research is reproducible, robust and translatable to support disease research utility for clinical research and development. One of the group’s major focuses is to provide quality resources and promote the publication of “negative” data—results of studies where researchers are not able to confirm or replicate experimental results which are often not submitted for publication.

“Science is a progressive and, at its essence, self-correcting, but we know it can be much more informative if both positive and negative data are published for all scientific to see,” said Dr. Magali Haas, CEO of CVB and co-chair of the U.S. branch of the GPDF. “Unfortunately, the scientific community is not motivated to publish ‘negative’ results, as they are not seen as advantageous for the scientist, organization and journal. This, unfortunately, is a disservice to the scientific community, as not sharing negative unpublished data is a waste of human capital and valuable resources and can lead to the duplication of efforts by others in the field. In fact, the estimated costs of this ‘lost’ science in the U.S. alone is $28 billion annually.”

The closing date for submissions was April 21, just a couple weeks after the announcement that they had opened, but if you are interested in the competition (to be announced Sept. 12) or want to submit something for next year, visit www.preclinicaldataforum.org for more information.

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

BY RANDALL C. WILLIS

As little as a decade ago, sitting through any session of the AACR or ASCO conferences, one could not help but be struck by the activity and potential for immunotherapies. What started as a trickle of monoclonal antibody (mAb) therapies in the late 1990s became a steady flow in the 2000s and a torrent in the 2010s.

But even as more biotherapeutics were approved and more companies explored the space, the benchmarks of success rose almost as quickly as the price tags associated with treatment. And while the development of products like rituximab and trastuzumab could never be described as easy, many consider those first few antibody targets the low-hanging fruit of immuno-oncology.

In the push to enhance the precision of treatment or to develop follow-on biotherapies when the initial molecules cease to work, researchers have had to explore increasingly intractable targets that often represent increasingly smaller patient populations. The result of that extra work and those smaller markets is an increasing price tag that, in some cases, threatens to shift the cost-benefit analysis.

Unable to change the patient population, researchers are faced with having to increase the efficiency of antibody discovery and development, working to focus as much energy as possible on only those candidates with the best potential for success.

Higher-hanging fruit

“I’ll be very honest and say it’s hard for me really to understand how we’re going to address costs, primarily because the discovery of these drugs is not simple and it’s not getting any simpler,” admits John Proctor, senior vice president of marketing at Berkeley Lights. “For a long time, it was all about monoclonal antibodies, and there have been some amazing mAbs discovered,” he continues, adding that although people continue to explore mAb discovery, it is often with an eye toward combining antibodies as bi- or trispecific molecules.

That, he points out, has introduced a level of complexity that is only now being realized. It is simple math. “If you need two or potentially three antibodies to make one drug, then you need two to three times the number of campaigns than you...”
ANTIBODIES

CONTINUED FROM PAGE 17

did previously,” he says. “And, on top of that number of campaigns, you also have to be able to assess the diversity of antibodies generated against the particular target very quickly.”

For AbCellera CEO Carl Hansen, that perception of complexity has been an issue since the earliest days of the antibody therapeutics.

“If you roll back 30 years, therapeutic antibodies were not even on anyone’s radar,” he recounts. “In fact, when people first started doing them, the pharmaceutical industry dismissed it as being overly complex.

“Starting with some blockbusters in the 1990s, that field has grown into what is now probably north of a [$200 billion market and has been consistently, for decades, the fastest-growing class of therapeutics.”

From his earliest days as a professor at the University of British Columbia (UBC), however, Hansen has monitored the development of the field, seeing opportunities in computation, genomics and microbiology to address biomedicai challenges.

“One of the dynamics we saw as the field has progressed was that pharmaceutical companies were being increasingly pushed toward targets that had proven to be difficult using conventional technologies,” he says.

For Hansen, the best way to address these challenges was not to head to the bench to re-engineer what Mother Nature had perfected over 350 million years. Rather, he saw a need for methods that produced a better immune response and then to better screen that response to find the best molecules.

Another factor, he notes, was the birth of the biotech industry and the growth of specialized fields such as immuno- oncology, which has significantly layered on complexity to an already challenging task.

“These companies either have a new angle on biology or they have technologies that typically require some elements of antibody to make them work,” Hansen explains. “It could be CAR T. It could be bispecific. It could be antibody-drug conjugates.”

It was in recognizing the changing landscape that Hansen’s academic interests took a more commercial turn.

“In 2012, we recognized that we could wrap those technologies together to make a best-in-world platform for searching deeply into natural immune systems to find antibodies that had the properties that made them suitable for development as therapeutics,” he recounts.

At the core of this advance was a focus on single-cell analysis.

“Single-cell analysis was a theme that I worked on for over a decade,” Hansen says. “This was an opportunity to apply single-cell analysis to what is by far one of the most interesting things in biology: adaptive immunity. It is also one where the connection to a real problem in the industry—finding the next generation of drugs—allowed us to build a thriving business.”

Part of seizing on this opportunity meant seriously rethinking the technologies and methods that got the field to this point. Central to that was wondering if the limitations of hybridoma technology— a founding method of antibody discovery and development—had surpassed its benefits.

“Aaron Winters and colleagues at Amgen Research and UBC offered their take on hybridomas in a recent paper,” Hansen notes. “The efficiency of immortalizing antibody-secreting cells through fusion with myeloma cells is quite low, they suggested. Even with optimized electrofusion protocols, as few as one in 5,000 input B cells manages to not only survive fusion, but also become immortalized and secrete antibody.

“Additionally, hybridoma methods generally require extensive cell culture, which is labor intensive and dependent on monios, further slowing development timelines,” the authors continued.

This challenge, they argued, can lead to the identification of low-affinity antibodies, and often requires multiple rounds of resource-intensive affinity maturation to generate potent molecules. In some ways, Hansen suggests, those limitations were acceptable in the early days because of the targets that researchers were tackling.

“Thirty years ago, that was fine,” he remarks. “There were easy targets, there wasn’t a lot of competition, and all you needed to find was any old antibody that happened to bond the target and block it.”

Hansen adds that another bonus was that it was pretty easy to mount immune responses against the chosen targets.

“Hybridoma, for that reason, has been the cornerstone from which we have had the blockbusters that we do today,” he continues.

“One of the big advantages of hybridoma is that it allows you to go after antibodies from natural immune responses, as compared to synthetic approaches—e.g., doing yeast or phage display—and they have been much more successful in getting through to the clinic,” he recalls. “I think 80 percent or more of the antibodies that have been approved have come from immunizations or from natural sources.”

However, Hansen is quick to highlight the inherent limitations of what he calls the Franken-cell approach and the loss of more than 99 percent of what was available in the animal starting material.

Implementing plan B

“If you care about diversity, which is the thing that we really emphasize in our program, it is important to have a large number of antibodies so that you’re not just picking any antibodies that work, but rather you are picking the one that is most potent and has the properties that make it most quickly and easily developable into a drug,” Hansen notes. “You want to make sure that you cast as wide a net as possible.”

“We are in a numbers game,” adds Marian Rehak, vice president of research and development at Sphere Fluidics. “If you want to screen the whole repertoire, you need the technology that allows you to do that.”

With such challenges in mind, Winters and colleagues heralded the advent of microfluidic and microencapsulation technologies that permit the direct identification and characterization of antibody-secreting B cells.

“These micro tools eliminate the need for immortalization, are species-agnostic, allow high-throughput sampling as well as multiparameter phenotyping of the input cells, have reduced reagent consumption compared to hybridoma and display technologies, and maintain the ability to retain the native VH and VL pairings of the original antibody,” they noted.

Earlier this year, Rehak and colleagues at Sphere Fluidics and UBC described the application of Cyto-Mine in both antibody discovery and cell line development. In this proof-of-concept experiment, antibody-secreting CHO cells were monitored rather than hybridomas or B cells.

As the authors described, the process is basically broken down into four steps.

Initially, using a biocompatible surfactant, both cells and assay reagents are encapsulated with culture medium into picodroplets. These picodroplets, which can carry anywhere from zero to one to a few dozen cells as required, are then incubated to permit protein production and secretion.

Using a FRET-based assay to detect IgG production, picodroplet fluorescence is monitored and positive cells are collected and stored in a chilled microchamber or dispensed into a collection device, such as single cells into microrriter wells. Negative picodroplets, meanwhile, are diverted to waste.

The assay can be customized by the selection of appropriate FRET-based detection probes specific for the thing that we really emphasize in our program, it is important to have a large number of antibodies so that you’re not just picking any antibodies that work, but rather you are picking the one that is most potent and has the properties that make it most quickly and easily developable into a drug.”

Carl Hansen of AbCellera
the protein of interest, such as IgG, or for antigen-specific IgG using labeled antigen assays, Rehak and colleagues explained.

The picodroplets can then be interrogated a second time and verified for monoclonality.

“From all the experiments shown, there was no apparent difference in cell outgrowth rate between Cyto-Mine and manual [limiting dilution cloning],” the authors noted. “These data suggest that Cyto-Mine is a gentle and cell-friendly cloning technology.”

In this experiment, the picodroplets were approximately 450 pL in volume, which the authors suggested was about five to six orders of magnitude smaller than volumes used in assays done in a 96-well plate.

“This means that in the same time, the concentration of secreted antibodies from a single cell can be 5-6 orders of magnitude higher in picodroplets than in conventional vessels,” they explained. In a typical Cyto-Mine instrument run, between 100,000 and 40 million cells can be screened.

Thus, not only does the microfluidic system offer increased throughput at up to single-cell resolution, but also it offers significantly reduced reagent costs.

Rehak also points out that Cyto-Mine can be used to monitor cell-surface protein expression and even flag issues related to antibody misfolding and aggregation.

Winters and colleagues had similar experiences working with Berkeley Lights’ Beacon platform in a process the Amgen team described as NanOBlast.

“Amgen was one of the earliest customers of Berkeley Lights, and they have been super-supportive of our work in developing applications for biopharma, both in antibody discovery and in cell line development,” says Berkeley Lights’ Proctor.

Rather than sequester B cells and reagents into picodroplets, the Beacon system uses microfluidics to move cells, reagents, beads or other objects through the channels of a culturing microchip, and then optoelectronics to dispense single cells and reagents into any of hundreds or thousands of one-nanoliter reaction chambers called nanopens.

It is within these nanopens that the B cells produce antibodies, which can be assayed for IgG secretion or antigen-specific IgGs. Beyond these two basic assays, however, the system also allows researchers to perform more functional assays such as competitive binding, cell binding and ligand-receptor blocking. The key, according to Proctor, is to reveal functional characteristics as quickly as possible.

“If you’re able to ask basic questions, like ‘does this antibody bind my target,’ that’s informative,” he states. “But if you then have to re-express and do all of this analytical characterization downstream on, say, 1,000 antibodies because you weren’t able to assess function to find out you only have 100 on the backend, you’ve probably invested months of work and hundreds of thousands of dollars trying to answer that question.”

“Because we can do these functional assays on-chip up front during the primary screen, we can ANTIBODIES CONTINUED ON PAGE 20
find all 1,000 or however many hits would be target binders, but we could then tell you a priori that there's only actually 100 functional ones.”

This effect was highlighted in a recent application note where 33,377 mouse plasma B cells were screened for binding to PD-L1 beads, resulting in 598 positives. These were then screened for binding to PD-L1 expressed on the surface of CHO cells, reducing the positive hits to 273. A subsequent ligand-receptor blocking assay demonstrated that 46 leads not only bound PD-L1, but also blocked the interaction between fluorescently tagged PD-1 and PD-L1.

Thus, performing these assays within the same chip reduced the deeper characterization effort from 600 potential leads to 46.

Key to the platform and to maintaining cell viability are the optobeads.

“At a very high level, we are using broad-spectrum light to activate a series of optical switches on a siliconized chip,” explains Proctor. “When we use light on that chip, the switches are essentially able to turn on and off.”

When that switch is on, Proctor continues, it creates a dielectric force that essentially repels an object, whether it’s a micro bead or a cell.

“If you just draw a box around it, so that there’s a force on all four sides, then you can move the box and the cell or object stays inside the box, and you can direct it wherever you would like on the chip,” he adds.

This progress in high-throughput B cell analysis, however, doesn’t mean that hybridomas have been completely abandoned.

**Hybridoma hold-outs**

“We are seeing movement from hybridoma to B cells, but recently, we have also seen movement back to hybridomas,” says Rehak.

And many biopharma companies have long used and extensively validated hybridoma approaches.

Last year, Scott Dessain and colleagues at the Lankenau Institute for Medical Research, FDA’s Center for Biologies Evaluation and Research, and Children’s Hospital of Pennsylvania acknowledged the opportunities still afforded from the technologically straightforward methods.

“They produce full-length, glycosylated mAbs that maintain their original heavy chain-light chain pairings without the need for recombinant gene expression,” the authors explained.

“However, their major shortcoming is that mAbs are secreted into the cell culture medium, so that hybridomas must be maintained in oligoclonal pools while their secreted mAbs are analyzed separately,” they acknowledged.

“This impedes the discovery of rare mAbs because it imposes practical limits on the numbers of cells that can be analyzed, and is a disadvantage compared to yeast display methods, in which mAbs are expressed on the cell surface and can be screened for antigen binding in bulk culture.”

Rather than abandon hybridomas, however, Dessain and colleagues looked for ways to mimic the cell surface expression capabilities of yeast display within the hybridoma screen. The result is the platform On-Cell mAb Screening (OCMS).

“OCMS transiently captures and displays mAbs on the hybridoma surface, while preventing mAbs from binding to cells that do not secrete them,” the authors explained.

The system relies on an anchor-linker strategy, whereby an anchor protein—an anti-rabbit IgG tandem scFv—is expressed in the fusion partner cell line and is maintained in the hybridoma. This is complemented with a rabbit anti-human IgG antibody (RAH) linker.

When RAH is added to the culture, it binds to the surface of the hybridoma cells, where it captures antibodies secreted by the cell to which it is bound. Excess RAH in the culture medium acts as a competitor to prevent secreted antibodies from one cell binding to neighboring hybridoma cells.

This provides specificity to the reaction, so that mAbs secreted by cells within a heterogeneous population can be analyzed individually in association with the cells that make them,” Dessain and colleagues suggested. “Cells expressing mAbs with desired features can be identified by fluorescence imaging techniques.”

By mixing cells with different binding properties, the researchers showed that a given mAb was only bound by the cells that secreted that mAb. Beyond fluorescence microscopy, the researchers also demonstrated the utility of their platform with flow cytometry.

The researchers also noted how the analogy with yeast display extended beyond antibody capture at the cell surface.

“High-throughput competitive binding, epitope complementarity, and dissociation rate assays developed for yeast should be adaptable for screening mAbs expressed by OCMS hybridomas,” they proposed. “OCMS can also be used to assess mAb expression levels by individual cells in a heterogeneous population in real time, using either fluorescence imaging or flow cytometry.”

“This feature should be useful to establish and monitor stable, high-expressing cell clones for master cell banks and bioreactor production runs.”

Earlier this year, the technology was licensed from Lankenau to be commercialized by new company OCMS Bio, for which Dessain serves as chief scientific officer.

Identifying and characterizing cells that produce antibodies against specific targets is still a long way from having something that will work as an immunotherapy, however. Given that an antibody for clinical treatment faces many different stresses and strains than one in its natural immune environment, other molecular facets must be explored to determine whether a given molecule can be developed into a therapeutic.

**Developability and design**

“The question of developability is an important one,” says Hansen.

Recognizing parallels with Lipinski’s Rules of Five in the small-molecule space, he suggests there are several metrics that they examine in the antibody space.

“In fact, there are many more rules that have to do with how well it expresses, solubility, predictions of PK, chemical instability and the like,” he offers.

In 2019, Charlotte Deane and colleagues at University of Oxford, MedImmune, Roche, GlaxoSmithKline (GSK) and UCB Pharma set out to computationally define developability guidelines for anti-body profiling by correlating protein sequences of 242 post-Phase-1 therapeutics with their biophysical properties.
“Using the distributions of these properties, we built the Therapeutic Antibody Profiler (TAP), a computational tool that highlights antibodies with anomalous values compared with therapeutics,” the authors described. “TAP builds a downloadable structural model of an antibody variable domain sequence and tests it against guideline thresholds of five calculated measures likely to be linked to poor developability.”

Based on previous work, they focused their attention on the complementarity-determining regions (CDRs) and metrics involving the surface hydrophobicity, positive and negative charges of the CDRs, length of the CDRs, and asymmetry in the net heavy- and light-chain surface charges.

Once the researchers created a red-, amber- and green-flag labeling system, they tried to reproduce in silico the real-world developability experiences of clinical antibody candidates.

Using datasets supplied by MedImmune, the researchers examined the anti-NGF antibody MEDI-578, which showed minor aggregation issues that were significantly aggravated during affinity maturation to MED-1912.

“TAP assigns MEDI-578 an amber flag and MED-1912 a red flag—by a large margin—in the CDR vicinity PSH metric,” Deane and colleagues noted. “The paper describes how back-mutation of three hydrophobic residues in the anti-NGF antibody MEDI-578 to those of MEDI-1912 to those of MEDI-578 led to MEDI-1912STT, fixing the aggregation issue while maintaining potency. TAP assigns MEDI-1912STT no developability flag.”

They then examined issues with protein expression, starting with anti-IL13 candidate AB008, which offered no developability issues until it was affinity matured to AB001. Offering poor levels of expression, AB001 was further modified via sequence modification to AB001DDEN, which restored expression levels.

“TAP assigns no developability flags to AB008 but a red flag to AB001 and an amber flag to AB001DDEN for its CDR vicinity PNC metric, again red-flagging the candidate with prohibitive developability issues,” the researchers noted.

Pleased as Deane and colleagues were with their findings, they were quick to note the inherently limited scope of the TAP guidelines.

“For example, they will not detect sources of immunogenicity or more subtle mechanisms that lead to poor stability,” they suggested. “Nevertheless, we have shown that the TAP guidelines can selectively highlight antibodies with expression or aggregation issues.”

Beyond these biophysical developability issues, Hansen sees so much more arising from sequence analysis.

“The sequence base is so diverse that very often it is not simply a matter of liabilities, but starting to be able to read the protein sequence to infer more complex properties that generally apply to antibodies,” he says. “That’s one of the things that we’re working on in our platform.”

Working with partners over the last few years, he continues, AbCellera has identified, sequenced, cloned and expressed hundreds of thousands of antibodies. That database allows the company to learn which features of antibodies are ones that make them more likely to express well or be more soluble, and to help with the question of developability.

“In the end, what it really comes down to for any target is that if you can do a much deeper search of the natural immune system and more effectively and efficiently harness the total diversity, then, as you take those hundreds or thousands of molecules through the various tests that help you predict which one will be a good drug, you can stand the attrition,” Hansen explains.

“You can leap the ones that don’t have the right properties behind and still make sure that you have a robust pipeline that gets all the way to the end so that you have multiple leads that you can finally bring into clinical trials.”

The reduced candidates achieved with lower-throughput systems like hybridoma or other microclonal systems, he contrasts, reduce your chances of finding antibodies with the right potency or developable properties.

“In the end, what that means is we’re able to scan that diversity every time to do the screen.”

John Proctor of Berkeley Lights

“Even just immunizing the same target over and over, you’ll see different immune responses. By accessing all compartments, we’re able to scan that diversity every time to do the screen.”

John Proctor of Berkeley Lights

Looking to reduce this process even further, companies like Trianni have developed transgenic mouse lines that produce fully human antibodies directly.

For some targets or functional epitopes, however, evolutionary conservation between humans and mice can make it difficult to mount an immune response, explained Torben Gjetting and colleagues at Symphogen (now part of Servier) in 2019.

“One solution to overcome this limitation is to use divergent animal species that are evolutionarily more distant to mammals,” the authors wrote, introducing the chicken as one such species. “Chickens may not only be able to raise antibodies against very conserved targets, but also to find leads against heretofore intractable targets, there is growing interest in looking beyond the usual sources.”

“The lion’s share of discovery is still done from rodents,” says AbCellera CEO Carl Hansen. “Of course, there are wildtype rodents, but there are methods for taking antibodies from a rodent and then humanizing them into an antibody that looks like a human antibody.”
SPECIAL REPORT

As AbCellera CEO Carl Hansen notes, “In 2012, we recognized that we could wrap [various] technologies together to make a best-in-world platform for searching deeply into natural immune systems to find antibodies that had the properties that made them suitable for development as therapeutics.” Pictured here is the company’s leadership team.

As AbCellera CEO Carl Hansen notes, “In 2012, we recognized that we could wrap [various] technologies together to make a best-in-world platform for searching deeply into natural immune systems to find antibodies that had the properties that made them suitable for development as therapeutics.”

CONTINUED FROM PAGE 21

ANTIBODIES

CONTINUED FROM PAGE 21

that you need to start circling back and doing protein engineering, and that leads to inefficiencies and delays in getting to the clinic,” he notes.

 Seeing the whole board

AbCellera recognized early on that it isn’t enough to have a screening platform, Hansen says. Rather, you have to work on all of the steps.

Thus, the company spent considerable time and effort learning how to generate antigens and get good immune responses, which form the input for the screening platform.

“If you don’t get the right input, it’s unlikely you’re going to find what you’re looking for in a drug,” he states.

“Once you’ve done that for many targets and you have a throughput like ours—we can easily screen through a million cells in an afternoon—then the challenge is no longer can I find an antibody against my target, but rather how can I get the most information content in that screen,” he suggests.

Those screens allow them to go from those thousands of hits down to a much smaller and manageable number—say, 100—that have the other properties important to turning a lead into a drug.

Hansen offers the example of a screen to determine not only if an antibody binds to the target, but also to look at cross-reactivity against eight different targets at once.

“That can help when you want to find an antibody you can test in a non-human primate or in other animals,” he explains. “It can also help when you want an antibody that hits one receptor but misses another isoform.”

“We can do experiments to select for antibodies that have higher affinity, that recognize certain epitopes, that block ligands,” he continues. “There is a lot of functional information that can be gained.

Each piece of information advises the next step of moving through development, starting with cloning, moving through expression, and into further testing that is simply better performed in microtiter plates. According to Hansen, “I don’t think you’re ever going to be able to do all of those at the single-cell level. I think you want to bring some number through so that you’re doing your tests in a rigorous way.”

In March, however, Berkeley Lights announced their effort to try to expand what was possible at the single-cell level, introducing OptoCell Line Development 2.0. In support of this effort, Jennitte Stevens and colleagues at Amgen Research recently used GFP- and RFP-expressing CHO cells to compare clonality assurance with the Beacon platform and industry-standard FACS-assisted cell deposition and limiting dilution seeding.

“When comparing between growing colonies, the Beacon cloning and confirmation process calls 94 percent of exported cultures as positive that they were clonally derived,” the authors noted. “This is compared to 45 percent for a FACS and 17 percent for a limiting dilution process.”

“Additionally, Beacon clones that have been selected for export into 96-well microtiter plates have a higher recovery rate (56 percent) (positive + negative / attempts) compared to FACS (24 percent) and limiting dilution (33 percent) in the same plate format,” they added.

Whatever the method used, the ability to screen broader repertoires of cells earlier and more thoroughly, and failing or adjusting tempting candidates without expending as many resources, is sure to change the landscape of antibody development and immunotherapy more broadly from initial exploration to, perhaps, a patient’s bedside.

“We are in a numbers game. If you want to screen the whole repertoire, you need the technology that allows you to do that,” says Marian Rehak of Sphere Fluidics.

The researchers also tested Sym021 for its ability to activate T cells in vivo and its impact on tumor growth in four mouse models.

“Sym021 treatment was found to induce significant tumor growth inhibition in several syngeneic tumor models and even complete tumor eradication in the Sa13 murine fibrosarcoma model,” they reported.

Given these results, Sym021 was further subjected to toxicology testing in cynomolgus monkeys and is currently in a Phase 1 clinical trial as a monotherapy or in combination with anti-LAG-3 or anti-TIM-3 leads vs. solid tumor malignancies or lymphomas.

To the authors’ knowledge, this was the first in-human study of a chicken-derived therapeutic e.g., spleen, lymph nodes and bone marrow—which cannot be equally accessed by all methods.

For example, B cells from bone marrow have not been historically amenable to fusion with myeloma cells to form hybridomas, explains John Proctor, senior vice president of marketing at Berkeley Lights.

“They seem to be overly sensitive to the process and don’t survive,” he continues. “So, hybridoma for a long time has been limited to just splenocytes.” Likewise, immunization and epitope localization can differ across the immune compartments and thereby produce a different immune response.

“Even just immunizing the same target over and over, you’ll see different immune responses,” Proctor adds. “By accessing all compartments, we’re able to scan that diversity every time to do the screen.”

Given the increasing complexity and demand of newer immunotherapy approaches, starting with the broadest array of options can only help to increase the chances of success.

WIDE

CONTINUED FROM PAGE 21

also against novel human functional epitopes that are masked in mice due to sequence conservation,” they continued. “Furthermore, antibodies against human targets generated in chicken are often cross-reactive to the mouse orthologous target.”

To test their thinking, the researchers generated a large antibody repertoire against the immune checkpoint protein PD1 in chickens. They then humanized the antibodies and compared the best candidates for PD1 binding affinity and functional activity to the commercial anti-PD1 immunotherapies pembrolizumab and nivolumab.

“The epitope of Sym021 was particularly interesting since it allowed for exceptionally strong cross-reactivity to both human, cynomolgus monkey, and mouse antibody.

Alternatively, you may switch species to explore antibodies structurally distinct from those in humans, such as cameldids.

“They have antibodies that have a single heavy chain, and that allows you to have a single polypeptide that can be generated within the animal’s immune system, which specifically recognizes the target and makes it very amenable to protein engineering,” Hansen explains.

“One of the big advantages of camelid antibodies is that they are modular and can be combined with simple linkers and protein engineering methods to make a variety of different molecular constructs that would otherwise be very challenging to produce and to manufacture,” he adds.

But even without changing species, the full antibody repertoire is spread across the multiple immune compartments—
THN102 reduces sleepiness for Parkinson's patients

LYON, France—A Phase 2 trial of THN102 in Parkinson’s disease ended positively for Theranex, with the drug candidate meeting its primary endpoint of significantly reducing excessive daily sleepiness in Parkinson’s disease patients. THN102 was tested against placebo at two dosage levels: THN102 200mg modafinil/2mg fencaine and THN102 200mg modafinil/18mg fencaine. Patients who received THN102 200/2 had an improvement of 3.9 points on the Epworth Sleepiness Scale compared to 2.4 points for placebo, and the number of patients no longer experiencing excessive daytime sleepiness for the duration of treatment was 27.5 percent for the THN102 200/2 group vs. 16.2 percent for the placebo group. In addition, tolerability was excellent, with no impact on other motor disorders or symptoms.

Two positive studies for Incyte

WILMINGTON, Del.—April saw Incyte report on Phase 3 data from its TRuE-AD program for ruxolitinib cream in patients with mild-to-moderate atopic dermatitis at the Revolutionizing Atopic Dermatitis Virtual Symposium. The primary endpoint for the Phase 3 TRuE-AD1 and TRuE-AD2 studies was the proportion of patients who achieved Investigator’s Global Assessment (IGA) Treatment Success (IGA-TS), defined as an IGA score of 0 (clear) or 1 (almost clear) with at least a two-point improvement from baseline, at Week 8. Both studies met their primary endpoint, with significantly more patients achieving IGA-TS with ruxolitinib compared to a vehicle non-medicated cream. It also had a substantial, sustained effect on itch. Dr. Jim Lee, Incyte’s group vice president, Inflammation & AutoImmunity, said the company plans to submit an NDA for ruxolitinib later this year.

Antibody therapeutic from Compugen demonstrates no dose-limiting toxicities

BY ILENE SCHNEIDER

HOLON, Israel—Compugen Ltd., a clinical-stage cancer immunotherapy company specializing in predictive target discovery, presented updated results from its ongoing Phase 1 dose-escalation study of COM701 at the 2020 American Association for Cancer Research (AACR) Virtual Annual Meeting 1 in April. COM701 is a first-in-class anti-PD-1 antibody being evaluated in patients with advanced solid tumors who have exhausted all available standard therapies. Compugen is attempting to establish a predictive drug discovery infrastructure and to discover and develop novel therapeutic proteins and drug targets.

Demonstrating what the company called “encouraging signals of durable disease control,” COM701 was well tolerated with no dose-limiting toxicities observed, both as a monotherapy and in combination with Bristol-Myers Squibb’s Opdivo (nivolumab). Additionally, COM701 demonstrated promising signs of anti-tumor activity with high disease control rate in both the monotherapy and combination therapy arms (69 percent and 75 percent, respectively). Those figures included two confirmed partial responses and durable responses of more than six months across cohorts, in the heavily pretreated patients enrolled in the study. Key findings presented by Dr. Ryan J. Sullivan, assistant professor of Medicine at Compugen is studying COM701 both as a monotherapy and in combination with Bristol-Myers Squibb’s Opdivo (nivolumab). Additional, COM701 demonstrated promising signs of anti-tumor activity with high disease control rate in both the monotherapy and combination therapy arms (69 percent and 75 percent, respectively). Those figures included two confirmed partial responses and durable responses of more than six months across cohorts, in the heavily pretreated patients enrolled in the study. Key findings presented by Dr. Ryan J. Sullivan, assistant professor of Medicine at...

Optimal OPTICs

ADVM-022 demonstrates efficacy, durability in OPTIC trial in wet AMD

BY KELSEY KAUSTHVEN

REDWOOD CITY, Calif.—While the COVID-19 pandemic has slowed or halted many clinical trials, causing delays in enrollment or complicating patient treatments, some trials are still advancing. One such study is Adverum BioTechnologies Inc.’s OPTIC Phase 1 trial of ADVM-022, which recently reported new interim clinical data as well as an update on ongoing enrollment.

ADVM-022 is a gene therapy being developed as a treatment for wet age-related macular degeneration (AMD). It uses a proprietary vector capsid, AAV7m8, carrying an aflibercept coding sequence under the control of a proprietary expression cassette.

The OPTIC Phase 1 trial is a multi-center, open-label, dose-ranging trial evaluating the safety and tolerability of a single intravitreal dose of ADVM-022 in patients with wet AMD who are responsive to anti-vascular endothelial growth factor (VEGF) treatment. Patients in Cohorts 1 and 4 will receive ADVM-022 at a dose of 6 x 10^11 vg/eye, though Cohort 4 will receive prophylactic eye drops instead of the oral steroids in Cohort 1. Similarly, patients in Cohorts 2 and 3 will receive ADVM-022 at a dose of 2 x 10^11 vg/eye, with patients in Cohort 3 receiving prophylactic eye drops and Cohort 1 receiving oral steroids. The primary endpoint is safety and tolerability after a single intravitreal injection, and enrollment is underway for Cohort 4.

More skin in the game

Libtayo shows promise for a second indication

BY MEL J. YEATES

TARRYTOWN, N.Y. & PARIS—Regeneron Pharmaceuticals Inc. and Sanofi S.A. recently reported top-line data from a Phase 2 trial for Libtayo in patients with advanced basal cell carcinoma (BCC) who had progressed on, or were intolerant to, prior hedgehog pathway inhibitor (HHI) therapy. Libtayo demonstrated clinically meaningful and durable responses.

“Like other PD-1 inhibitors, Libtayo (cemiplimab) is a fully human monoclonal antibody targeting the immune checkpoint receptor PD-1 on T cells. By binding to PD-1, Libtayo has been shown to block cancer cells from using the PD-1 pathway to suppress T-cell activation,” says Matthew Fury, executive medical director of Clinical Sciences in Oncology at Regeneron.

“Regeneron and Sanofi were the first to recognize the potential of PD-1 inhibition to treat non-melanoma skin cancers like basal cell carcinoma and cutaneous squamous cell carcinoma (CSCC). These cancers have some of the highest tumor mutational burdens among all cancers, and we hypothesized that they would be particularly responsive to PD-1 inhibition,” Fury continues. “This led us to investigate Libtayo in pivotal trials for both advanced BCC and CSCC. Our trials in advanced CSCC were the first to have results and have supported multiple global approvals for Libtayo in this indication, where it is now the standard of care.”

 COMP701 CONTINUED ON PAGE 24
IL-6

CONTINUED FROM COVER

critical if they required mechanical ventilation, high-flow oxygenation or ICU treatment. Preliminary analysis of the Phase 2 portion of the trial demonstrated that Kevzara rapidly lowered C-reactive protein—a key marker of inflammation—and met the primary endpoint. Baseline levels of IL-6 were elevated across all treatment arms, with higher levels observed in critical patients. No new safety findings were observed.

"Even in a pandemic setting, it’s both crucial and possible to obtain controlled data in adequately sized trials to provide the evidence needed to inform optimal medical care. Emerging evidence with Kevzara and other repurposed drugs in the COVID-19 crisis highlights the challenges of making decisions about existing medicines for new viral threats using small, uncontrolled studies," said Dr. George D. Yancopoulos, co-founder, president and chief scientific officer of Regeneron. "We await results of the ongoing randomized clinical trials to learn more about COVID-19 and better understand whether some patients may benefit from Kevzara treatment. In addition, there is an acute need for tailoring approaches to patients who have specifically targeted this virus. To that end, Regeneron is rapidly advancing our targeted anti-SARS-CoV-2 antibody cocktail, and we plan to initiate clinical trials in June."

Analysis of clinical outcomes in the Phase 2 trial was exploratory, and focused on the severe and critical groups. In the preliminary analysis, Kevzara had no notable benefit on clinical outcomes when comparing severe and critical groups versus placebo. However, there were negative trends for most outcomes in the severe group and positive trends for all outcomes in the critical group. Following a review by an independent data monitoring committee (IDMC) of all available Phase 2 and Phase 3 data, the trial will be immediately amended so that only critical patients continue to be enrolled to receive Kevzara 400 mg or placebo.

"Targeting the correct patient population and severity group is vital when conducting any study. However, testing a variety of severity groups in this trial allowed a process of elimination to help understand the relationship between the cytokine response in COVID-19 patients, and more importantly, when to treat with IL-6 inhibitors (or in this case, when not to treat)," points out Angad Lotay, an infectious diseases analyst at GlobalData. "In order to draw more conclusive evidence, Sanofi and Regeneron are proceeding with [the] Phase 3 portion of the Phase 2/3 trial, specifically targeting critically ill patients at a dose of 400 mg. This will provide a more accurate demonstration as to whether there is a relationship between the use of IL-6 modulators and the most severe COVID-19 patients."

"Although it is known that IL-6 is a key cytokine mediator in CRS [cytokine release syndrome], its onset and peak timing can vary in different diseases. It is important to evaluate the relationship between the peak level and time of serum cytokines to ultimately optimize treatment timing. Sanofi and Regeneron now have some data on that, and the results of the Phase 3 Kevzara trial will provide a better understanding of this pattern in COVID-19 patients," Lotay adds. After the IDMC review, Regeneron and Sanofi conducted a review of the discontinued severe group that revealed the negative trends in Phase 2 (n=126) were not reproduced in Phase 3 (n=276). Clinical outcomes were balanced across all treatment arms, and outcomes for the severe group were better than expected based on prior reports, regardless of treatment assignment; e.g., in the Phase 2 portion approximately 80 percent were discharged, 10 percent died and 10 percent remained hospitalized.

"As we quickly follow the science to better understand this disease and explore how best to treat patients, these initial results from the randomized clinical trial setting provide physicians much-needed insights and information regarding Kevzara for patients with COVID-19," says Dr. John Reed, global head of research and development at Sanofi, regarding preliminary results from a trial being conducted along with Regeneron.

Regeneron and Sanofi began evaluating Kevzara for COVID-19 in March, in collaboration with the Biomedical Advanced Research and Development Authority, the U.S. government's investment arm, and hospitals across the country. The Phase 2/3 trial has an adaptive design with two parts and expects to enroll up to 400 patients. The first part recruited patients with severe COVID-19 infection across approximately 16 U.S. sites, and evaluated the impact of Kevzara on fever and patients' need for supplemental oxygen. The second, larger part of the trial will evaluate the improvement in longer-term outcomes, including recovery from death. Both segments are investigating the need for mechanical ventilation, supplemental oxygen and/or hospitalization.

ENDNOTE: E062018

CLINICAL TRIALS

COM701

CONTINUED FROM PAGE 23

Harvard Medical School and faculty member of the Termeer Center for Targeted Therapy and Immunotherapy Programs at Massachusetts General Hospital Cancer, showed that COM701 was well tolerated through 20 mg/kg IV Q4 weeks as a monotherapy and 10 mg/kg IV Q4 weeks in combination with Opdivo (480 mg IV Q4 weeks). No dose-limiting toxicities were reported, no increased toxicity was observed in the combination arm, and no patients discontinued treatment because of the toxicity of any study drug. Sullivan said that preliminary COM701 pharmacokinetic data supports IV Q4 weeks dosing, allowing the dosing schedule with Opdivo.

Half the patients (six of 12) in the combination arm remain on study, some with continued responses observed beyond 200 days of treatment. Across all patients, there were durable responses of stable disease for over six months in six of 28 (21 percent) patients. The two patients previously reported with confirmed partial responses—one from the monotherapy arm (microsatellite stable primary peritoneal cancer) and one from the combination arm (microsatellite stable colorectal cancer)—remain on treatment.

As Sullivan commented in his presentation, "There is a high need, and need for the treatment of patients who are refractory to or relapse following treatment with checkpoint inhibitors. COM701 is a novel first-in-class humanized IgG4 monoclonal antibody that binds with high affinity to PVRIG, a novel immune checkpoint discovered computationally by Compugen, blocking its interaction with its ligand PVRIL2. We have previously reported on the preliminary antitumor activity of COM701 monotherapy. We are now reporting the preliminary safety and antitumor activity of COM701 in combination with nivolumab (Arm B), and we provide data update in COM701 monotherapy dose cohorts (Arm A)."

"With a highly refractory and comorbid patient population, this trial enrolled patients that are difficult to treat, including those who progressed on numerous prior therapies," he added. "Achieving durable disease control, including partial responses, is remarkable in this population, and I am particularly enthusiastic about the proportion of patients in the combination arm—currently 50 percent—who remain on treatment. Taken together, these results support further investigation of targeting PVRIG with COM701, and suggest that targeting the PVRIG/TIGIT pathways may broaden the selection of indications for the monotherapy expansion cohorts."

"COM701 proved to be well tolerated and with a manageable safety profile as monotherapy and in combination with nivolumab. Currently, COM701 monotherapy dose-escalation arm is enrolled, and completion in the combination dose-escalation arm at 20 mg/kg is ongoing. The monotherapy expansion cohorts that will follow the monotherapy dose-escalation arm is based on a biomarker-informed selection of indications, and will include non-small cell lung cancer, ovarian, breast, endometrial and colorectal cancer," Sullivan concluded.

ENDNOTE: E062001

CONNECT:

JUNE 2020
The data presented were current as of the cutoff date of April 1. Adverum noted that ADVM-022 has demonstrated ongoing efficacy and durability, with no rescue injections needed in six of six patients in Cohort 1, and no rescue injections needed in eight of 11 patients in Cohort 2. The safety profile is favorable, with only mild-to-moderate adverse events and no evidence of vasculitis, retinitis or choroiditis. Inflammation has been observed, but it has responded to steroid eye drops, and a six-week course of eye drops has in fact led to fewer adverse events and less inflammation than a 13-day prophylactic regimen of oral steroids. Patients in Cohort 3 have presented with early anatomic and vision improvements, including a reduction in central retinal thickness and a mean best-corrected visual acuity gain of +6.8 letters.

“I am pleased to say that all of the OPTIC data continues to support what we have previously reported, including robust efficacy and evidence of a dose response from a single injection of ADVM-022; further evidence of long-term durability, with all Cohort 1 patients now out beyond one year and zero rescue injections; and lastly and importantly, a favorable safety profile,” Leone Patterson, president and CEO of Adverum, remarked in a company webcast regarding the OPTIC results.

Dr. Arshad M. Khanani, director of clinical research at Sierra Eye Associates and a principal investigator in the OPTIC trial, said, “It’s impressive to see the long-term durability demonstrated at the higher dose of ADVM-022 in a patient population that previously required frequent injections to maintain their vision, and are now beyond one year of follow-up with no rescue injections. Additionally, preliminary evidence in Cohort 3 shows vision and anatomical improvements, and that the six-week prophylactic steroid eye drop regimen is effective at minimizing early ocular inflammation. These are very positive data, and it is exciting to see that this intravitreal gene therapy has the potential to completely change the treatment paradigm for patients with wet AMD.”

Intravitreal injections of anti-VEGF are the current standard-of-care treatment for wet AMD, but they come with a high treatment burden—injectons are required every four to 12 weeks, and patient compliance can be difficult.

“We are encouraged by the robust efficacy signal and evidence of a dose response in the OPTIC trial with interim data from three cohorts. Also, momentum in OPTIC is strong, as we are currently enrolling patients in Cohort 4 at the higher dose of 6 x 10^11 vg/eye using the same steroid regimen as Cohort 3,” said Aaron Osborne, chief medical officer of Adverum. “We look forward to reporting additional data in the second half of this year from OPTIC. Beyond wet AMD, we are on track with our plans to advance ADVM-022 in diabetic retinopathy, our second indication, and we continue to expect to begin enrolling patients in our planned clinical trial in the second half of this year.”

Adverum Biotechnologies is developing its candidate ADVM-022 as a gene therapy for wet age-related macular degeneration (AMD).
Across both cohorts thus far, ProQR recently shared positive findings from an interim analysis of its Phase 1/2 STELLAR trial of QR-421a in adults with Usher syndrome and non-syndromic retinitis pigmentosa (uRPS) due to USH2A exon 13 mutations.

“The goal of the interim analysis of this 24-month STELLAR trial of QR-421a was to assess safety and early signs of efficacy for the purpose of informing next steps in development and future trial strategy,” said Dr. David Rodman, executive vice president of research and development of ProQR. “We are pleased with the current safety profile and are very encouraged by early signals of target engagement and clinical activity supported by concordant benefit observed across multiple outcome measures for 25 percent of QR-421a-treated patients thus far in this trial.”

“The findings support continuing the trial as planned, with both cohort expansion and dose escalation in order to identify a potential development path to registration. Importantly, these data represent the second program from our ophthalmology pipeline that is supported by preclinical predictions from human retinal organoids, providing further validation of our translational approach and platform technology.”

Key initial findings include the following:

• Across both cohorts thus far, QR-421a was observed to be generally well tolerated with no serious adverse events noted.

• In the six sham treated subjects (two followed for nine months and four for three months), outcome measures demonstrated no consistent pattern of response above the “noise” level. In contrast, two of eight QR-421a-treated patients (one each in the 50 µg and 100 µg moderate visual impairment at baseline (peripheral vision affected).

• One of four treated patients in the low-dose group was classified as a responder with onset of action observed by the 3 month visit. Benefit was maintained for six months or longer, which is consistent with the expected half-life of QR-421a in photoreceptors. This Usher syndrome patient was homozygous for USH2A exon 13 mutations and had dose cohorts) demonstrated benefit across multiple concordant outcome measures.

• One of four treated patients in the low-dose group was classified as a responder with onset of action observed by the 3 month visit. Benefit was maintained for six months or longer, which is consistent with the expected half-life of QR-421a in photoreceptors. This Usher syndrome patient was homozygous for USH2A exon 13 mutations and had
By Jeffrey Bouley

A s the Chinese general and philosopher Sun Tzu wrote centuries ago, “If you know the enemy and yourself, you need not fear the result of a hundred battles.” Honestly, while that sounds nice and has a ring of truth, it’s not always the case, and certainly not in battles with cancer.

It just seems as if the more we know about cancer, the more we find out that we don’t know nearly enough—and maybe that we never will fully understand it. And part of that, of course, is that cancer isn’t just one thing—there are myriad types with multitudes of different characteristics.

Still, though, even if we never seem to know enough and even if every time we peel back a layer we see several more seemingly incomprehensible ones beneath it, the more we know the better we are able to fight, even if we don’t always win.

To that end, here are several recent stories telling us more about what we know—or need to know—to better advance oncology research and development.

‘Uninhibited’ cells crowd the scene when this pathway goes awry

For all our social nature, people generally don’t like to be packed too tightly. Think crowded buses or subway trains with people trying to maintain their personal space as much as possible even with densely packed spaces. In the same way, noted researchers at Scripps Research in May, cells generally prefer not to be packed in too tightly. In fact, they have set up mechanisms to avoid this, a phenomenon called “contact inhibition.”

As Scripps points out, a hallmark of cancer cells is that they lack this contact inhibition, and instead become “pushy,” facilitating their spread. Unfortunately scientific understanding of the mechanism underlying this cell behavior change has had many gaps.

That might be on the verge of changing thanks to a new paper titled “Uninhibited” cells crowd the scene revisiting the pathway that cells use to coordinate whether or not they should grow and how quickly.

A key player is a protein called YAP, a regulator of gene expression. YAP is a major effector of a pathway referred to as the Hippo pathway. As Scripps points out, a hallmark of cancer cells is that they lack this contact inhibition, p27. But a disrupted Hippo pathway interferes with normal YAP behavior and blocks the expected p27 surge.

YAP and have a functional role in promoting cancer.

A key player is a protein called YAP, a regulator of gene expression. YAP is a major effector of a pathway referred to as the Hippo pathway. As Scripps points out, a hallmark of cancer cells is that they lack this contact inhibition, p27. But a disrupted Hippo pathway interferes with normal YAP behavior and blocks the expected p27 surge.

Kissil and the rest of the team were surprised to find YAP in the uncharacteristic role of shutting down gene transcription. Previous studies suggested that YAP is an activator of genes that promote cell growth. The reality proved to be much more complex.

“The way we show here is that YAP can also turn off genes, not just turn them on,” Kissil says. “It shuts down genes that would otherwise prevent cells from proliferating.”

When we target YAP in cancer, we are targeting its function as an activator of cancer, but we now know we also need to consider its suppressive functions, as well,” Kissil said. “We have to consider both the activation and the repression.”

Finding the players that both interact with YAP and have a functional role in promoting cancer growth required use of a genome-wide bioinformatics technique called ChiP-seq.

The team worked specifically in human Schwann cells, which are peripheral nerve cells that produce the insulating myelin around nerves, but the findings should apply to other cancers, Kissil thinks.

The researchers looked at YAP in the context of cell crowding and learned that YAP’s role involves recruitment of other interacting proteins that include YY1, also known as Yin-Yang 1, EZH2 and a protein complex called PRC2.

Those will also be important to study further, Kissil noted, as well as the interaction of these players in the context of cancer drug resistance.

Is CD40 the key to three-drug combos in immuno-oncology treatments?

Emerging three-drug combinations are poised to redefine the immune-oncology treatment paradigm in advanced malignancies with high unmet need, according to data and analytics company GlobalData, adding CANCER CONTINUED ON PAGE 28
that the oncology market is “saturated” with new drugs that target the immune system; “however, these only target part of the problem caused by cancer’s ability to hide from the immune system.”

Noted Miguel Ferreira, an oncology and hematology analyst at GlobalData: “To achieve the full potential of this strategy, new targets that independently trigger immune activation in addition to blocking cancer-mediated suppression of the immune system are needed.”

One of the current strategies using checkpoint inhibitors in certain cancer types involves treating with a PD-1 inhibitor, which blocks the ability of the cancer to silence necessary immune cells, and adding a second drug, such as an angiogenesis inhibitor, to help stabilize the response by disrupting the tumor microenvironment.

What is currently missing is a third component, a drug targeting a co-stimulatory T-cell receptor which must directly and independently activate T cells to initiate an immune response.

“CD40 has been identified as the leading stimulatory receptor in T cells that would allow for a three-drug combination strategy by being the agent involved in directly activating the immune response,” said Ferreira. “As a single drug treatment, the dose required to get a sufficient effect might be too high and therefore too toxic but when used in combination, a lower dose can contribute to the potential synergism between drugs targeting different aspects of the immune system against cancer.”

Protein power vs. tumor growth and damage

Purdue University scientists have created a new therapeutic option that may help halt tumor growth in certain cancers—such as prostate cancer—which is among the most common types of cancer in men. Not only that, but it might fix damage done by tumors during their rampage.

“We have designed a therapy that can help recruit immune cells to kill cancer and also help repair bone and tissues damaged by tumors,” said Dr. Marxa Figueiredo, an associate professor of basic medical sciences in Purdue’s College of Veterinary Medicine, who helped lead the research team and is working with the Purdue Research Foundation Office of Technology Commercialization to patent the innovation. “One of the best features of this technology is that it shows great promise in enabling treatment for many other cancers and diseases that could benefit from halting tumor growth and promoting bone repair.”

The therapy technology is presented in the journal Molecular Therapy: Methods & Clinical Development in a paper titled “Ligand-Mediated Targeting of CytokineInterleukin-27 Enhances Its Bioactivity In Vivo.”

The Purdue team used a protein called interleukin-27, or IL-27, which has shown promise in reducing tumor growth and helping stop cancer from spreading in the body. IL-27 is a cytokine, a kind of protein secreted by cells of the immune system that act as chemical messengers and can help the immune system target cancer and other diseases.

“Immune cells are naturally attracted to areas of the body with lots of signals that come from proteins such as IL-27,” Figueiredo said. “So, with our novel approach of targeting the IL-27 to the tumor or bone cells, we can take advantage of these signals to bring healthy cells to areas of the body with cancer or other disease and kill the tumors and begin the process of repairing bone and other musculoskeletal tissues.”

Figueiredo said the new Purdue therapy technology has applications for people and animals with many different types of cancer—including breast and lung—and other diseases where protein targeting could improve the immune system’s response.

A warning of cellular stress: an explanation for chemotherapy resistance

Mitochondria, tiny structures present in most cells, are known for their energy-generating machinery. Now, Salk Institute researchers have discovered a new function of mitochondria: they set off molecular alarms when cells are exposed to stress or chemicals that can damage DNA, such as chemotherapy. The results, published online in Nature Metabolism on Dec. 9, 2019, could lead to new cancer treatments that prevent tumors from becoming resistant to chemotherapy.

“Mitochondria are acting as a first line of defense in sensing DNA stress. The mitochondria tell the rest of the cell, ‘Hey, I’m under attack, you better protect yourself,’” said Dr. Gerald Shadel, a professor in Salk’s Molecular and Cell Biology Laboratory and the Audrey Geisel Chair in Biomedical Science.

Most of the DNA that a cell needs to function is found inside the cell’s nucleus, packed in chromosomes and inherited from both parents. But mitochondria each contain their own small circles of DNA (called mitochondrial or mtDNA), passed only from a mother to her offspring. And most cells contain hundreds—or even thousands—of mitochondria.

Shadel’s lab group previously showed that cells respond to improperly packaged mtDNA similarly to how they would react to an invading virus—by releasing it from mitochondria and mounting an immune response that beefs up the cell’s defenses.

In the new study, Shadel and his colleagues set out to look in more detail at what molecular pathways are activated by the release of damaged mtDNA into the cell’s interior. They homed in on a subset of genes known as interferon-stimulated genes (ISGs), which are typically activated by the presence of viruses. But in this case, the team realized, the genes were a particular subset of ISGs turned on by viruses. And this same subset of ISGs is often found to be activated in cancer cells that have developed resistance to chemotherapy with DNA-damaging agents like doxorubicin.

To destroy cancer, doxorubicin targets the nuclear DNA. But the new study found that the drug also causes the damage and release of mtDNA, which in turn activates ISGs. This subset of ISGs, the group discovered, helps protect nuclear DNA from damage—and, thus, causes increased resistance to chemotherapy drug. When Shadel and his colleagues induced mitochondrial stress in melanoma cancer cells, the cells became more resistant to doxorubicin when grown in culture dishes and even in mice, as higher levels of the ISGs were protecting the cell’s DNA.

“Perhaps the fact that mitochondrial DNA is present in so many copies in each cell, and has fewer of its own DNA repair pathways, makes it a very effective sensor of DNA stress,” Shadel theorized.

Most of the time, he points out, it’s probably a good thing that the mtDNA is more prone to damage—it acts like the proverbial canary in a coal mine to protect healthy cells. But in cancer cells, it means that doxorubicin—by damaging mtDNA first and setting off molecular alarm bells—can be less effective at damaging the nuclear DNA of cancer cells.

“It says to me that if you can prevent damage to mitochondrial DNA or its release during cancer treatment, you might prevent this form of chemotherapeutic resistance,” Shadel says. His group is planning future studies on exactly how mtDNA is damaged and released and which DNA repair pathways are activated by the ISGs in the cell’s nucleus to ward off damage.

Sci舀entists continue to try to figure out all the ins and outs of cancer—and they may never come to an end of the road there. But every new step makes fighting cancer easier even if it adds complications to research and development efforts.

Cells prefer not to be crowded and stop proliferating once too densely packed. A technique called proximity ligation analysis reveals an interaction between two proteins (YAP and YY1) in the nuclei of human Schwann cells. YAP and YY1, working together, can shut off this behavior. The red dots represent the interaction, nuclei are stained in blue.
JUPITER, Fla.—Sooner or later, most cancer patients develop resistance to the very chemotherapy drugs designed to kill their cancer, forcing oncologists to seek alternatives. Even more problematic, once a patient’s tumor is resistant to one type of chemotherapy, it is much more likely to be resistant to other chemotherapies as well, a conundrum long known as multidrug resistance. Once patients reach this point, the prognosis is often poor, and for the last 35 years scientists have attempted to understand and block multidrug resistance in cancer by using experimental medicines.

A new study from scientists at Scripps Research in Florida raises red flags about this strategy. Inhibiting the key gene involved in cancer drug resistance has unintended side effects on specialized immune system cells called CD8+ cytotoxic T lymphocytes (CTLs), the team found. This could dull anticancer immune responses, and potentially increase vulnerability to infection, since CTLs are “killer” T cells, essential in the fight against both viral and bacterial infections and tumors, said lead author Dr. Mark Sundrud, an associate professor of immunology and microbiology at Scripps Research.

Several genes are now recognized for contributing to multidrug resistance in cancer, but the first and most prominent of these is called multidrug resistance-1 (MDR1). Its discovery more than three decades ago set off a race to develop drugs that would inhibit expression of MDR1. But those MDR1 inhibitors have consistently disappointed in clinical trials. The reasons behind these failures have remained enigmatic.

In a new study published in April under the title “Physiological expression and function of the MDR1 transporter in cytotoxic T lymphocytes” in the Journal of Experimental Medicine, Sundrud and colleagues suggest that the repeated failure of MDR1 inhibitors in human cancer trials may be due to a previously unrecognized—and essential—function of the MDR1 gene in CD8+ cytotoxic T lymphocytes.

Using new genetic approaches to visualize and functionally assess MDR1 expression in mouse cells, the team found that CTLs were unique in their constant and high-level expression of MDR1. In addition, preventing MDR1 expression in CTLs, or blocking its function using inhibitors previously tested in human cancer trials, sets off a chain reaction of CTL dysfunction, ultimately disabling these cells from fighting off viral or bacterial infections.

Considering that these cells are also necessary for warding off most cancerous tumors, blocking MDR1 with existing inhibitors could also cripple natural immune responses to cancers, Sundrud says.

“With the help of our collaborators at New York University Medical Center, we looked at mouse immune cells from five major lymphoid and nonlymphoid tissues: bone marrow, thymus, spleen, lung and small intestine,” Sundrud says. “It became clear that the types of cells that are key to fighting infections and cancers, are among those most sensitive to blocking MDR1 function.”

It has been known for decades that CTLs, as well as “natural killer” cells, a type of white blood cell, express high levels of the MDR1 gene. But because MDR1 has historically been viewed only through the lens of creating multidrug resistance in cancer cells, few researchers thought to ask what MDR1 does during normal immune responses; those that did found confusing and often contradictory results, Sundrud says, likely due to the use of non-specific animal model systems.

Convinced that MDR1 might impact natural immune responses, Sundrud and colleagues sought to devise more specific mouse models to directly visualize and functionally characterize MDR1 expression in vivo. Additional experiments revealed that blocking MDR1 function hampered the earliest stages of the CTL response to infections, when these cells multiply rapidly to reach the numbers needed to kill all viral and bacterial invaders. In line with this result, MDR1 inhibition also affected long-lived immunity to infections that have been previously seen and eradicated. It also affected the cells’ energy organelles, called mitochondria.

“We think that MDR1 plays a special role in helping mitochondria provide energy to growing cells,” Sundrud says. “So, if you take this away, it makes sense that these cells can’t support the metabolic demand of cell division, and that they ultimately die.”

On one hand, Sundrud says, the research raises questions about the safety and utility of using systemic MDR1 inhibitors as cancer therapies. At the same time, the work reveals important new mechanisms that determine how the immune system fights off infections and develops long-lived memory.

“These insights become all the more pertinent today, given all the questions and concerns related to immunity against the pandemic coronavirus that causes COVID-19,” Sundrud says. The team is now looking to use this new knowledge to finally nail down a unifying function of MDR1 in all cells, whether it is in CTLs responding to infections, or cancer cells trying to deal with chemotherapeutic agents. In the shorter term, Sundrud and colleagues plan to explore new approaches to redesign existing MDR1 inhibitors to specifically target only cancer cells.

According to findings coming out of Scripps Research in Florida, some methods of dealing with cancer might actually inhibit the immune system’s ability to fight off tumors.

Treating cancer drug resistance may harm the immune system
Commentary: CRISPR screening in B cells—A primary tool for target discovery

Dr. Nicola McCarthy, Horizon Discovery

CRISPR has been hugely influential in drug development research and has enabled scientists to identify genes relevant to specific biological pathways. Further down the pipeline, CRISPR could help to reduce the risk of clinical trial failures, by helping to select compounds with a higher chance of success and stratify patient populations to determine which therapeutics will be most effective.

Dr. Nicola McCarthy of Horizon Discovery

CRISPR-mediated gene editing and screening capability in Bregs. As mentioned, Bregs produce IL-10, a cytokine implicated in the onset of autoimmune disorders and in the generation of an immune suppressive tumor microenvironment. Having established a protocol to drive primary human B cell differentiation to Bregs in vitro, we carried out a pilot arrowed CRISPR screen in these cells to find genetic regulators of IL-10 production, using the production of IL-10 as the end point of the screen. However, the impact of IL-10 in human disease is due to its effect on other cell types. Thus, co-culture assays can also be used as a screening endpoint, in particular looking for genes whose loss in Bregs inhibits their capacity to suppress the proliferation of T cells.

It is anticipated that conducting CRISPR screens in Bregs could identify genes that affect the function of B cells and other immune cell types, and provide insight into the critical role of these cells in cancer and autoimmune diseases, such as lupus, multiple sclerosis and rheumatoid arthritis.

Dr. Nicola McCarthy is manager of the Screening Business Unit at Horizon Discovery

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

REFERENCES
DIGNOSTICS

A better test for COVID-19

Digital PCR solution cuts down on false negatives, may help in clinical trials

BY JENNIFER CLIFFORD

Fluidigm Corporation and Next Gen Diagnostics (NGD) announced that its digital PCR solution, the Naica system, is readily available to all research centers and hospitals involved in the fight against COVID-19.

Currently, SARS-CoV-2 infections are being diagnosed through a method called real-time reverse transcription polymerase chain reaction (RT-PCR), which can fail to detect lower viral loads. This happens in cases where patients are mildly infected or in cases of defective sampling, causing some COVID-19 patients to test negative for the SARS-CoV-2 virus.

The Naica System reportedly offers a more accurate and sensitive method than RT-PCR, making it possible to cut down on the false negative results that currently hamper efforts to contain the re-emergence of the disease.

Since the beginning of the pandemic, more than 15 key Chinese institutions (including the Disease Control & Prevention, the First Affiliated Hospital of Zhengzhou University and others) have been using the solution developed by Stilla Technologies and reportedly have been able to successfully carry out advanced testing for the detection of SARS-CoV-2 in more than 1,200 samples from patients for whom RT-PCR tests were giving unsatisfying results. This, as well as the rapid launch of the Naica System, was made possible by investor TusPark Holdings and a collaboration with ApexBio/Cycloud.

“We are proud to be part of the fight against COVID-19. Our close collaboration with Apexbio, our partner in China, allowed us to quickly develop a solution to detect COVID-19 through digital PCR, by using our Naica system. This solution was launched last February by Apexbio in China and in mid-March by Stilla in Europe,” said Rémi Dangla, co-founder and CEO of Stilla Technologies.

ApexBio/Cycloud, which has been on the forefront of medical innovation during the outbreak in China, has been using the Naica System for years and quickly saw the benefits of digital PCR over standard RT-PCR. Stilla Technologies donated a total of three Naica systems to China, and these and other systems deployed there before and during the outbreak allowed advanced testing for the detection of SARS-CoV-2.

In addition to more accurate testing, Stilla also hopes the Naica System can benefit clinical trials for treatments of COVID-19 by providing a reliable and precise monitoring of the viral load in patients. Compared to standard RT-PCR, the quantification of the virus is said to be absolute and reproducible, across patients and across test sites, without the need for reference material and standard curves. The company’s ongoing developments aim to provide a complete solution which can detect a high number of virus variations.

NAICA CONTINUED ON PAGE 32

Putting the ‘AI’ in diagnostics

A look at the growing trend of integrating artificial intelligence and machine learning with diagnostics

BY KELSEY KAUSTINEN

Artificial intelligence (AI) has growing appeal in the field of drug discovery and development, offering the ability to process more information faster and possibly with less margin of error than human efforts. While many companies are applying this technology in pursuit of new drug targets for disease, some are looking to its utility in diagnosing those diseases.

The hope is that with the aid of high-throughput technologies scanning and comparing hundreds or thousands of cases for similarities and outcomes, disease states and progression can be better predicted and managed.

Dascena Inc. is one such firm betting on that approach, pursuing early disease intervention through better and earlier diagnosis. The company, which recently emerged from stealth mode, announced in the second quarter of 2020 that it had closed a $50 million Series B financing led by Frazier Healthcare Partners, with participation from Longitude Capital, existing investor Euclidean Capital and an undisclosed investor.

Dascena plans to use the funds to advance its portfolio of machine-learning algorithms meant to inform patient care strategies and improve outcomes.

AI CONTINUED ON PAGE 32
NAICA CONTINUED FROM PAGE 31
samples to support the current end of lockdown strategies and monitor the disease.
“Naica digital PCR is easy to use and provides higher sensitiv-
ity and reliability. We installed one Naica system in early March, and we use it for COVID-19 testing,” said a customer in the Hunan CDC.
“We have one Naica system and we use it for COVID-19 research at this moment to help [with] defeating infections,” reported another customer at the Virology Institute.
The Naica System is a highly sensitive digital PCR solution that runs on the company’s next-generation testing and nucleic acid quantification technology, Crystal Digital PCR, with the ability to characterize multiple types of nucleic acids with its three-color detection capability. Its ease of use and fast time to results—about two hours and 30 minutes—set this innovative technology apart in the digital PCR market.

SELUX CONTINUED FROM PAGE 31
antibiotics than current AST tech-
ologies—and, due to its ready expan-
sion to the market, we recently incorpo-
rate newly approved drugs. [It] will transform infectious disease patient care by expediting cures, improve-
patient outcomes, and reducing hospitalization and antibiotic infections. Truly transforming the way we prescribe and treat infec-
tious disease patients requires that we test using the right tools.
The $9.6-million award is the third funding tranche Selux has received from BARDA as part of the company’s milestone-based contract, which is worth up to $45 million. Selux has received $30.4 million in funding to date.
“BARDA has offered strong sup-
port in bringing forth the Selux NGP platform, and has led the way in the successful government-pri-
vate sector collaboration to solve one of the world’s greatest challenges—antibiotic resistance,” noted Luklin. “This leadership is especially vital now, as new data indicate the antibiotic resistance crisis is even more threatening than previously understood.”
“Although of course impacted by the COVID environment, we are currently involving clinical trials and we recognize those are more critical now, considering we have patients dying of secondary infections,” says Lukin. “We have high expectations for success in our current AST clinical trials, we will proceed with commer-
cialization to bring the technology to market for use in hospitals and health systems. We are advancing as quickly as possible with the full support of BARDA and our private investors, who recognize Selux’s potential to transform infectious disease patient care and combat the global crisis of antibiotic resistance.”
In November 2019, the Centers for Disease Control (CDC) released “Antibiotic Resistance Threats in the United States,” a study which found that antibiotic-resistant bacteria and fungi cause more than 2.8 million infections and 35,000 deaths in the U.S. every year. The study discovered that the mounting global threat of antibiotic resistance is much worse than previously known, with new research revealing that there have been “nearly twice as many annual deaths from antibiotic-resistant infections as CDC originally reported in 2013.”
Despite the change in today’s treatment para-
digm, deaths from superbugs will surpass deaths from cancer by 2050. “I think it’s exciting that we may be on the way to addressing our global crisis in antimicrobial resis-
tance. Between a recent new study revealing the global antibiotic resis-
tance crisis is made investments more than we thought, and the secondary bacte-
rial infections we are seeing caused by COVID-19, efforts to drive AST innova-
tion are more urgent than ever. I think people are starting to understand that we must preserve the efficacy of broad-spectrum anti-
biotics by shifting toward personal-
ized medicine,” said Lukin, who concludes, “Assuming success of our current NGP platform through clinical trials, we are excited to look forward to a high-throughput, low-cost, patient-
centered blood culture method.”

AI CONTINUED FROM PAGE 31
AI, as a result, we believe in the power of machine learning to improve patient care and out-
comes, and we continue to develop-
ment in digital PCR, this collaboration has made China Stilla’s second larg-
est market. In addition, Stilla has partnerships with several companies in Europe and the United States, including Hôpi-
tal Européen Georges Pompidou (HEGP) and Hôpital Bichat, that are deeply involved in the COVID-19 fight.
“Data and AI technology allows researchers to make dPCR a lab commodity for all areas of the life sciences. As an added bonus, the company actively advises and supports its customers worldwide with a multidisciplinary R&D team that boasts expertise spanning from microfluidics to chemistry, including molecular biology and artificial intelligence. The Stilla/Apexbio-part-
nership began a few years ago when Stilla was looking for distributors in Asia. Apexbio has experience in life-sciences instrumentation, and they were already experienced with digi-
tal PCR. This collaboration has made China Stilla’s second larg-
est market. In addition, Stilla has partnerships with several companies in Europe and the United States, including Hôpi-
tal Européen Georges Pompidou (HEGP) and Hôpital Bichat, that are deeply involved in the COVID-19 fight.
“Data and AI technology allows researchers to make dPCR a lab commodity for all areas of the life sciences. As an added bonus, the company actively advises and supports its customers worldwide with a multidisciplinary R&D team that boasts expertise spanning from microfluidics to chemistry, including molecular biology and artificial intelligence. The Stilla/Apexbio-part-
nership began a few years ago when Stilla was looking for distributors in Asia. Apexbio has experience in life-sciences instrumentation, and they were already experienced with digi-
tal PCR. This collaboration has made China Stilla’s second larg-
est market. In addition, Stilla has partnerships with several companies in Europe and the United States, including Hôpi-
tal Européen Georges Pompidou (HEGP) and Hôpital Bichat, that are deeply involved in the COVID-19 fight.
“Data and AI technology allows researchers to make dPCR a lab commodity for all areas of the life sciences. As an added bonus, the company actively advises and supports its customers worldwide with a multidisciplinary R&D team that boasts expertise spanning from microfluidics to chemistry, including molecular biology and artificial intelligence. The Stilla/Apexbio-part-
nership began a few years ago when Stilla was looking for distributors in Asia. Apexbio has experience in life-sciences instrumentation, and they were already experienced with digi-
tal PCR. This collaboration has made China Stilla’s second larg-
est market. In addition, Stilla has partnerships with several companies in Europe and the United States, including Hôpi-
tal Européen Georges Pompidou (HEGP) and Hôpital Bichat, that are deeply involved in the COVID-19 fight.
“Data and AI technology allows researchers to make dPCR a lab commodity for all areas of the life sciences. As an added bonus, the company actively advises and supports its customers worldwide with a multidisciplinary R&D team that boasts expertise spanning from microfluidics to chemistry, including molecular biology and artificial intelligence. The Stilla/Apexbio-part-
nership began a few years ago when Stilla was looking for distributors in Asia. Apexbio has experience in life-sciences instrumentation, and they were already experienced with digi-
tal PCR. This collaboration has made China Stilla’s second larg-
est market. In addition, Stilla has partnerships with several companies in Europe and the United States, including Hôpi-
tal Européen Georges Pompidou (HEGP) and Hôpital Bichat, that are deeply involved in the COVID-19 fight.
“Data and AI technology allows researchers to make dPCR a lab commodity for all areas of the life sciences. As an added bonus, the company actively advises and supports its customers worldwide with a multidisciplinary R&D team that boasts expertise spanning from microfluidics to chemistry, including molecular biology and artificial intelligence. The Stilla/Apexbio-part-
nership began a few years ago when Stilla was looking for distributors in Asia. Apexbio has experience in life-sciences instrumentation, and they were already experienced with digi-
tal PCR. This collaboration has made China Stilla’s second larg-
est market. In addition, Stilla has partnerships with several companies in Europe and the United States, including Hôpi-
tal Européen Georges Pompidou (HEGP) and Hôpital Bichat, that are deeply involved in the COVID-19 fight.
“Data and AI technology allows researchers to make dPCR a lab commodity for all areas of the life sciences. As an added bonus, the company actively advises and supports its customers worldwide with a multidisciplinary R&D team that boasts expertise spanning from microfluidics to chemistry, including molecular biology and artificial intelligence. The Stilla/Apexbio-part-
nership began a few years ago when Stilla was looking for distributors in Asia. Apexbio has experience in life-sciences instrumentation, and they were already experienced with digi-
tal PCR. This collaboration has made China Stilla’s second larg-
est market. In addition, Stilla has partnerships with several companies in Europe and the United States, including Hôpi-
tal Européen Georges Pompidou (HEGP) and Hôpital Bichat, that are deeply involved in the COVID-19 fight.
“Data and AI technology allows researchers to make dPCR a lab commodity for all areas of the life sciences. As an added bonus, the company actively advises and supports its customers worldwide with a multidisciplinary R&D team that boasts expertise spanning from microfluidics to chemistry, including molecular biology and artificial intelligence. The Stilla/Apexbio-part-
nership began a few years ago when Stilla was looking for distributors in Asia. Apexbio has experience in life-sciences instrumentation, and they were already experienced with digi-
tal PCR. This collaboration has made China Stilla’s second larg-
est market. In addition, Stilla has partnerships with several companies in Europe and the United States, including Hôpi-
tal Européen Georges Pompidou (HEGP) and Hôpital Bichat, that are deeply involved in the COVID-19 fight.
“Data and AI technology allows researchers to make dPCR a lab commodity for all areas of the life sciences. As an added bonus, the company actively advises and supports its customers worldwide with a multidisciplinary R&D team that boasts expertise spanning from microfluidics to chemistry, including molecular biology and artificial intelligence. The Stilla/Apexbio-part-
nership began a few years ago when Stilla was looking for distributors in Asia. Apexbio has experience in life-sciences instrumenta-

Stilla Technologies’ Naica digital PCR solution looks promising in terms of yielding better and more accurate diagnoses of SARS-CoV-2 infection, and the company hopes the Naica System can also benefit global patients by testing COVID-19 through digital PCR, by using our Naica system.
Rémi Dangla, CEO of Stilla Technologies

Knowledge Inference in Medical Image Analysis (KIMIA Lab) at Waterloo. “We showed it is possible using AI to detect COVID-19 without having access to a large archive. It is like putting many, many pathologists in a virtual room together and having them reach consensus.”
And the use of AI in diagnost-
cs—and indeed, in the industry in general—likely isn’t to be a pass-
ing fad, but a new standard. Pisia-
toia Alliance, a not-for-profit life-
sciences organization, recently shared its 2030 Life Sciences and Healthcare Roadmap, which stated “AI and machine-learning are transform-
ing AI and machine-learning in the pharmaceutical and life sci-
cences field. It notes that as of 2018, “more than a third of healthcare providers are already considering using AI in clinical settings.”
In order to leverage AI to analyze electronic medical records with a focus on new pre-
scriptions can catch physician errors and prevent issues such as overdose or other adverse events. According to John Wise, co-author of the report, it won’t be a fully digital future, but one where AI does the heavy lifting while human experts confirm the results. Allie Nawrat, a phar-
maceutical writer for GlobalData, noted that “The report predicts that in 2030 will be largely determined and improved by artificial intelligence (AI) … AI’s increasing role in diagnosis may be the best way to move us into being more like patient edu-
cators, responding to what the AI systems conclude.”

CONTINUE DIAGNOSTICS
A strong complement in China

Reaction Biology, PharmaCore Labs strike up collaboration agreement

BY KELSEY KAUSTIEN

MALVERN, Pa. & HAIMEN, China—Market expansion is the name of the game for a newly inked joint collaboration agreement between contract research organizations (CROs) Reaction Biology Corp. (RBC) and China-based PharmaCore Labs (PCL) Co. Ltd. Per the terms of the agreement, PCL will provide business support and development personnel to RBC, in addition to a staging facility for shipping compounds to the United States. In return, RBC will make its entire offering of biochemical, cell and in-vivo assay services available for PCL to distribute in China.

Dr. Haiching Ma, chief science officer of RBC, said, “While we have dozens of custom-common cancer types and special needs or immuno-oncology purposes.” He adds that RBC is a market leader specifically in kinase drug discovery services, epigenetic drug discovery, and the development of high-quality, specific assays.

“RBC has a unique portfolio of services. Since more and more Chinese companies are gearing up to do early-stage drug discovery, we believe the Chinese market will generate significant demand. PCL is one of the well-known CROs in China focusing on ion channel drug discovery and cardiac safety, with a client base covering over 50 percent of Chinese pharmaceutical research labs. Our list of contacts in this industry will want to hear more from RBC,” commented Dr. Howard Zhang, president of PCL.

Ma reports that RBC has more than 80 customers from China, consisting primarily of startup drug discovery companies and universities, as well as a few CROs. He says that drug discovery startups are on the rise in China, leading to increased demand for CRO services, pointing out that Reaction Biology fits this need very well.

“Based on a PharmaCore labs estimation, there are potentially over 500 companies and universities that have broad drug discovery programs, and we are connected with merely a small portion of them. Therefore, our interests in accessing this large potential market within China cannot be understated,” Ma remarks.

Ma tells DDN that China boasts “the fastest-growing drug discovery activity in the world, with strong financial supports in the healthcare business. China also has a large number of CROs and reagent companies that can all benefit from our services.”

“Our customer numbers in China have grown substantially in the past few years,” he adds. “There is an urgent need for us to be present in China not only to reach new customers, but also because helping our existing customers to fully utilize our high-quality services is of great import to us.”

According to Ma, this agreement is open-ended, but both companies expect it to be a long-term arrangement given the anticipated benefits.

“Both companies are providing pre-IND services with different focuses. There is no competition between the two companies—rather, we are more synergistic,” says Ma. “[Zhang’s] customers will greatly benefit from the broad range of services and unique products that RBC is able to provide. We can also introduce RBC’s large global customer base to his business and can access his special ion channel cell lines if needed for our customers. PharmaCore is located close to Shanghai, and this can provide BD and sale services to a large number of biotech companies in Shanghai and other Chinese cities, which is home to more than half of China’s drug companies and bio-startups.”

“Our customer numbers in China have grown substantially in the past few years. There is an urgent need for us to be present in China not only to reach new customers, but also because helping our existing customers to fully utilize our high-quality services is of great import to us,” Haiching Ma of RBC

With the familiarity of doing business in China and overseas, PharmaCore can help our customers to ship to and/or receive testing materials from our U.S. and Germany sites, which is a headache that some customers do not want to deal with. PharmaCore is able to help our Chinese customers in preparation of IND filing in China. Through PharmaCore, customers who may have no U.S. currency funding are still able to pay for our services with Chinese currency,” he concludes.
MAKING A DEAL ON ADCs
Trio Pharmaceuticals and Ajinomoto enter into development collaboration

BY DDN STAFF
SAN DIEGO & SAN FRANCISCO—This spring, Trio Pharmaceuticals Inc., a cancer therapeutics company developing novel antibody drugs (TRIObody and TRIObody Drug Conjugate, or TDC), and Ajinomoto Bio-Pharma Services, a leading provider of biopharmaceutical contract development and manufacturing services, announced a development agreement.

Under this deal, they will evaluate AJICAP, a proprietary site-specific conjugation technology offered by Aji Bio-Pharma for the development of TDC candidates. The AJICAP technology will be used to conjugate a cytotoxic payload to Trio’s lead oncology candidate, with Trio evaluating functionality of the TDC.

TDCs are a first-in-class kind of antibody-drug conjugate (ADC) with dual functionality that utilizes targeted payload delivery to stop both tumor growth and immunosuppression. By generating a less immunosuppressive tumor microenvironment, TDC reportedly enhances activation of tumor-specific immune effector cells, further facilitating cancer cell destruction. AJICAP is a site-specific conjugation technology compatible with various antibody modalities. AJICAP’s advantage is its “off-the-shelf” feature, allowing any antibody drug at any stage of development to be conjugated to drug payloads of choice without the need to modify the sequence.

“The AJICAP conjugation technology marks a new beginning in the ADC field, allowing generation of ADCs with site-specific conjugation without change in antibody sequence, a rate-limiting step in the development of site-specific ADCs,” said Dr. Shiva Bhowmik, CEO of Trio Pharmaceuticals. “Setting an early collaboration with Aji Bio-Pharma will ease our cGMP plans for clinical development.”

Trio Pharmaceuticals Inc. and Ajinomoto Bio-Pharma Services are working together regarding a first-in-class antibody-drug conjugate against cancer.

“The AJICAP conjugation technology marks a new beginning in the ADC field, allowing generation of ADCs with site-specific conjugation without change in antibody sequence.”
Dr. Shiva Bhowmik,
CEO of Trio Pharmaceuticals

YOUR REGULAR DOSAGE OF NEWS IN THE AREAS OF

- DISCOVERY
- RESEARCH & DEVELOPMENT
- PRECLINICAL
- CLINICAL TRIALS
- DIAGNOSTICS
- CONTRACT SERVICES
- BUSINESS & GOVERNMENT POLICY

For the pharma, biotech and life-sciences professional, understanding the complex process that results in new marketed therapeutics is an on-going challenge. In DDNews, you get insightful reporting and analysis of each stage in the pipeline—in print and online—from a staff of experienced life-science journalists. It’s an information resource you can’t find anywhere else.

Let’s start a dialog
Are there important issues, research areas or technologies you would like to read more about in DDNews? Let us know at Twitter (@DDNewsOnline) or friend us on Facebook.
**COVID-19 conversations**

International regulators met recently at a COVID-19 workshop organized by the European Medicines Agency (EMA) under the auspices of the International Coalition of Medicines Regulatory Authorities, which was co-chaired by the EMA and Health Canada. The purpose of the workshop was to discuss how data gathered during clinical practice and evidence from clinical trials of possible therapeutics or vaccines could bolster each other, with observational studies of real-world data in rounding out results from clinical trials. Participants shared insight into ongoing and pending trials, protocols and procedures, according to an EMA press release. Previous workshops covered vaccine development and compassionate use programs. As noted in the release, “These workshops underline the need and commitment by regulators to cooperate and improve information-sharing globally in relation to the research and development of treatments and vaccines against COVID-19.”

**Medigene expands patent portfolio**

MÜNCH & MARTINSREID, Germany—Medigene AG announced the receipt of two patents in April—one from the Japanese Patent Office (JP60/76/15) and one from the New Zealand Patent Office (NZ7/41/15)—covering the company’s CrossTag-1 technology. This platform enables cross-presentation of antigens (including MHC-I and MHC-II) in human leukocyte antigens (HLA) in humans. Medigene Immunotherapies GmbH and Helmholtz Zentrum München are co-applicants for the patents.

Prof. Detlev J. Schroeder, CEO and chief scientific officer of Medigene, said, “The granted patents are of particular relevance for the further development of our immunotherapies, as the novel technology assures that we can activate both helper T cells and cytotoxic T cells specific for peptides derived from the same cancer antigen. In patients, the interaction of both types of T cells is needed for best immunity to ultimately fight and control the cancer.”

**Germany’s Sartorius acquires selected assets of Danaher Life Sciences**

GOTTINGEN, Germany—Taking a big step toward broadening its pipeline for the development and production of biotech medicines, Sartorius closed on the acquisition of selected life-sciences businesses of Danaher Corp. on April 30. This multimillion-dollar acquisition reportedly will help Sartorius strengthen its lineup of downstream bioprocessing products, bringing it closer to providing a complete bioprocessing solution for the pharmaceutical industry.

“The acquisition of this portfolio is a further milestone for Sartorius,” says Joachim Kreuzburg, Sartorius executive board chairman and CEO. “The assets we purchased are an excellent strategic and operational fit with both our divisions. We are very pleased to welcome approximately 300 new Sartorius employees and to combine our expertise to become even more relevant together for our biopharma and life-sciences customers.”

**FDA updates trial guidelines**

Among other things, the new guidance for clinical trials clarifies management of protocol deviations and amendments.

BY DDN STAFF

SILVER SPRING, Md.—Just about everything seems to shift in terms of priorities, rules and limitations when it comes to the unfolding pandemic, so it should come as no surprise that U.S. FDA guidelines are a moving target as well.

In the latest development, the FDA has updated its guidance for performing clinical trials during the COVID-19 pandemic, and in that guidance the agency offers clarifications for managing protocol deviations and amendments. It also outlines the steps companies can take when they are considering patients getting experimental products at home instead of trial sites.

Finally, the updated guidance also contains three new questions and answers about the use of video conferencing for remote participant visits, for utilization of alternate laboratory or imaging centers, and regarding post-marketing requirements for medical devices and treatments. Interestingly about the first of those three items, the FDA reports that it does not consider this kind of video conferencing to fall under the category of electronic records that are subject to 21 CFR part 11, but rather as “a live exchange of information between the personnel and trial participants.”

For more details, go to the FDA website at www.fda.gov and look for the “FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency” document that was first issued in March 2020.  

**ON THE CUTTING EDGE**

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

**BROADENING ITS FOOTPRINT IN BIOTECH**

Sartorius paid a purchase price of $825 million for the acquisition and, since the execution of the purchase agreement on Oct. 19, 2019, has been preparing for integration of the acquired businesses into the two divisions of the Sartorius Group, Kreuzburg states. And despite the “special conditions,” Sartorius CEO Joachim Kreuzburg states. And despite the “special conditions”...

**Medigene expands patent portfolio**

MÜNCH & MARTINSREID, Germany—Medigene AG announced the receipt of two patents in April—one from the Japanese Patent Office (JP60/76/15) and one from the New Zealand Patent Office (NZ7/41/15)—covering the company’s CrossTag-1 technology. This platform enables cross-presentation of antigens (including MHC-I and MHC-II) in human leukocyte antigens (HLA) in humans. Medigene Immunotherapies GmbH and Helmholtz Zentrum München are co-applicants for the patents.

Prof. Detlev J. Schroeder, CEO and chief scientific officer of Medigene, said, “The granted patents are of particular relevance for the further development of our immunotherapies, as the novel technology assures that we can activate both helper T cells and cytotoxic T cells specific for peptides derived from the same cancer antigen. In patients, the interaction of both types of T cells is needed for best immunity to ultimately fight and control the cancer.”

**Germany’s Sartorius acquires selected assets of Danaher Life Sciences**

GOTTINGEN, Germany—Taking a big step toward broadening its pipeline for the development and production of biotech medicines, Sartorius closed on the acquisition of selected life-sciences businesses of Danaher Corp. on April 30. This multimillion-dollar acquisition reportedly will help Sartorius strengthen its lineup of downstream bioprocessing products, bringing it closer to providing a complete bioprocessing solution for the pharmaceutical industry.

“The acquisition of this portfolio is a further milestone for Sartorius,” says Joachim Kreuzburg, Sartorius executive board chairman and CEO. “The assets we purchased are an excellent strategic and operational fit with both our divisions. We are very pleased to welcome approximately 300 new Sartorius employees and to combine our expertise to become even more relevant together for our biopharma and life-sciences customers.”

**FDA updates trial guidelines**

Among other things, the new guidance for clinical trials clarifies management of protocol deviations and amendments.

BY DDN STAFF

SILVER SPRING, Md.—Just about everything seems to shift in terms of priorities, rules and limitations when it comes to the unfolding pandemic, so it should come as no surprise that U.S. FDA guidelines are a moving target as well.

In the latest development, the FDA has updated its guidance for performing clinical trials during the COVID-19 pandemic, and in that guidance the agency offers clarifications for managing protocol deviations and amendments. It also outlines the steps companies can take when they are considering patients getting experimental products at home instead of trial sites.

Finally, the updated guidance also contains three new questions and answers about the use of video conferencing for remote participant visits, for utilization of alternate laboratory or imaging centers, and regarding post-marketing requirements for medical devices and treatments. Interestingly about the first of those three items, the FDA reports that it does not consider this kind of video conferencing to fall under the category of electronic records that are subject to 21 CFR part 11, but rather as “a live exchange of information between the personnel and trial participants.”

For more details, go to the FDA website at www.fda.gov and look for the “FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency” document that was first issued in March 2020.  

**ON THE CUTTING EDGE**

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

**BROADENING ITS FOOTPRINT IN BIOTECH**

Sartorius paid a purchase price of $825 million for the acquisition and, since the execution of the purchase agreement on Oct. 19, 2019, has been preparing for integration of the acquired businesses into the two divisions of the Sartorius Group, Kreuzburg states. And despite the “special conditions,” Sartorius CEO Joachim Kreuzburg states. And despite the “special conditions”...
BIOTECH
CONTINUED FROM PAGE 35

prevailing during the pandemic crisis,” integration has already started, according to a company spokesperson. "For a long time, we have been pursuing the strategy of making our portfolio broader and more attractive for our customers in the biopharmaceutical industry—a very consistent continuation," says Andre Hofmann, Sartorius’ head of public relations. "As a result of the acquisition, the company’s broader offering will support customers even more comprehensively in the development of biotech medicines and vaccines, as well as in the safe and efficient production of such pharmaceuticals.”

According to Hofmann, “Investors responded positively to this deal,” but he notes that even more important is the positive feedback from customers, whom he points out increasingly demand seamless solutions between their various production steps. And that demand includes efforts related to the pandemic.

Since hardly any vaccine is produced without Sartorius technology or products, we already have an impact on the development of a vaccine against COVID-19,” Hofmann remarks. "For example, our customer CanSino Biologics and Beijing Institute of Biotechnology recently got approval for their vaccine candidate for COVID-19 to enter a Phase 2 clinical trial. The customer is using Sartorius’ Biostat® STR 200L bioreactors to prepare clinical samples.”

Moreover, demand for consumables for the production of medications and vaccines, as well as for diagnostic test kits, has been high within the first months of the year, he states.

Sartorius was able to seal the acquisition deal by taking advantage of an unexpected opportunity. “[Danaher] had to divest certain assets to close their deal to acquire the GE Life Science business,” Hofmann explains. “As this opportunity opened up, we sought talks at an early stage. The various requirements of the antitrust authorities in the different countries were high, so the matter took a few months. This is now the look in the rear-view mirror as we are looking forward to the integration, and together we will take advantage of the many opportunities that are now available to us.”

The businesses acquired by Sartorius generated revenue of approximately $170 million in 2019 and cover various laboratory and bioprocessing technologies that are complementary to the portfolio lines at Sartorius.

The businesses acquired by Sartorius generated revenue of approximately $170 million in 2019, and cover various laboratory and bioprocessing technologies that are complementary to the portfolio lines at Sartorius.

The businesses acquired by Sartorius generated revenue of approximately $170 million in 2019, and cover various laboratory and bioprocessing technologies that are complementary to the portfolio lines at Sartorius.

$170 million in 2019 and cover various laboratory and bioprocessing technologies that are complementary to the portfolio lines at Sartorius.

The businesses acquired by Sartorius generated revenue of approximately $170 million in 2019, and cover various laboratory and bioprocessing technologies that are complementary to the portfolio lines at Sartorius.

Q&A: The challenges of a vaccine for COVID-19

BY MEL J. YEATES

AS THE WORLD REACTS TO THE SARS-CoV-2 pandemic, one of the most pressing questions is, “When are we going to get a vaccine for this disease?” Scores of pharma companies have jumped into ramping up manufacturing capacities and developing vaccine candidates for COVID-19. But we’re not likely to see a successful vaccine until 2021 or later, causing many to wonder how the process can possibly take that long.

DDN: With Amélie Boulais, vaccine platform marketing manager at Sartorius Stedim Biotech, to learn about some of the obstacles that stand between our present circumstances and a vaccine for SARS-CoV-2.

DDN: What are some of the most pressing challenges for companies that are attempting to create a vaccine for COVID-19? Amélie Boulais: One of the first obstacles is deciding on an antigen and [a] platform for the vaccine candidate. There is no precedent for what will work best against this virus, so the industry is working on a variety of different approaches. So far, we have seen traditional viral vaccines, recombinant proteins, viral vectors, and mRNA and DNA emerge as some of the leading strategies.

Companies also need to consider how to ramp up manufacturing to an unprecedented speed, if their vaccine candidate is deemed safe and efficacious during clinical trials. To ensure availability of a vaccine in 2021, vaccines developers are already working on setting up production capacity. This means they will take a huge financial risk of producing a vaccine before the outcome of the clinical trials.

DDN: Why are we looking at a wait time of around 18 months before the first COVID-19 vaccine could become available? Boulais: A time of 18 months is already a very ambitious target. Vaccine development usually takes 10 years. Speed should not compromise efficacy nor safety. The vaccine must undergo extensive testing, and this will take several months. Researching, developing, testing, manufacturing and distributing a novel vaccine is a long and complex process. To focus on just two of these stages, there are inherent development and clinical trial challenges that cannot be readily bypassed.

On the development front, this vaccine will need to be safe and effective in every demographic category, regardless of age, gender or comorbidities. That’s difficult to achieve and to prove—especially as we’re starting from scratch. The industry is better prepared for a new influenza vaccine, for example, because seasonal influenza occurs every year. There is a template to build off. With SARS-CoV-2, there were no vaccines in development before this year, so everything from the platform to the antigen must be scrutinized.

When it comes to clinical trials, vaccine studies are lengthy for several reasons. The vaccine will be administered to healthy people, who are then monitored over time to determine whether they contract the disease. So, it’s not like treating a disease—we’re waiting for the person to be naturally exposed to the virus. Regulatory bodies are working to accelerate these clinical trials where possible, but patient safety must come first. That’s particularly challenging at this scale: to identify a side effect that occurs in 0.01 percent of the population, tens of thousands of patients will need to be identified, enrolled, inoculated and followed for results.

DDN: What are some of the bioprocess management challenges that may crop up while a therapy undergoes the production process? Boulais: Production will need to be scaled up quickly, so developers will need to strike a strategic balance between speed and overall process productivity. A number of solutions are available to accelerate process development, such as high-throughput development tools and experiment software that is designed to allow for a systematic approach to process development. Process intensification technologies can be implemented to compensate for low productive cell lines or limit the size of bioreactors during scale-up.

Process robustness is also important as production is scaled up, and should not be compromised by speed. This can be achieved through advanced sensors and process analytical technologies that may be combined with data analysis. Multivariate data analysis can be used to build statistical models to get an overview of the data, identify the reasons of deviations, and predict the properties of data. This can help to accelerate scale-up and de-risk tech transfer, while ensuring process robustness.

DDN: Approximately how long will it take to ramp up manufacturing of a vaccine once one is developed? Boulais: It is hard to say for sure at this time. Given the urgency, a lot of effort and money...
is being invested in the rapid scale-up of manufacturing. Some have proposed the idea of establishing large-scale manufacturing for promising candidates before they have been approved. [This] would likely waste billions of dollars producing vaccines that will never be used. However, it would also give the world a head-start on manufacturing the vaccines that do prove effective. We also know that manufacturers will need to rely on single-use technologies because they can be implemented and validated much faster than traditional stainless-steel facilities. These technologies are flexible, so they can keep up with the changing demand that is likely to come with vaccines. It is also important that developers work with an experienced bio-processing partner that can ensure a quality

“Production will need to be scaled up quickly, so developers will need to strike a strategic balance between speed and overall process productivity ... Process robustness is also important as production is scaled up, and should not be compromised by speed.”

Amélie Boulais of Sartorius Stedim Biotech

supply of single-use technologies.

The production of the COVID-19 vaccine will rely on partnership. Vaccine developers do not have time to build manufacturing capacities dedicated to COVID-19 manufacturing. They will partner with established vaccine manufacturers and contract manufacturing organizations that already have production capacities for similar processes and are heavily based on single-use technologies. This is why the vaccine candidates based on manufacturing platforms, such as viral vectors or mRNA, are so attractive. Once the vaccine is launched out of these existing repurposed facilities and is successful, the companies might consider building dedicated production capacities.

**DDN: What do you find most pressing to work on, to ensure the success of a vaccine against COVID-19?**

Boulais: Vaccine development has traditionally taken longer than 18 months, so this is an ambitious goal. There are still no approved vaccines for HIV (identified in 1981), SARS (outbreak began in 2003) and MERS (outbreak began in 2012). Developers and manufacturers are working as quickly as they can to develop a vaccine against the virus, but it is important to also maintain safety and efficacy standards. Partnership among universities and start-ups with promising candidates, established vaccine companies with experience in running clinical trials and regulatory filling, [and] contract manufacturing organizations and suppliers is essential to bring a vaccine to the market quickly. We need to bring all of our expertise together.

**EDGE CONTINUED FROM PAGE 35**

that trial sponsors incorporate a diversity of patient voices and rethink their approach to protocols, design and other parts of the trial that could benefit from patient input,” said Harry Glorikian, CEO of TLS. “By using a tool like TPC, the pharma and biotech companies gain capabilities to help speed up the process while satisfying key guidelines and reducing the overall trial cost.”

Now, having covered some technology that’s a bit more novel in terms of function and approach, we have a few more things to cover among the workhorses of traditional day-to-day work of pharma and life sciences, so keep reading to see if it’s something you need in your lab.

**Superior separation for high-order aggregates and macromolecules**

KING OF PRUSSIA, Pa.—Tosoh Bioscience LLC, a provider of chromatographic solutions for the separation of biomolecules, announced recently the introduction of TSKgel UP-SW Aggregate size exclusion chromatography (SEC) columns.

As the company pointed out in the announcement, antibody therapeutics are enjoying high growth rates, with the major areas of therapeutic application being cancer and immune/inflammation-related disorders like arthritis and multiple sclerosis. With that in mind, Tosoh noted, “Today, new antibody formats are entering clinical phases, with some of the new formats having a higher molecular weight than conventional antibodies. The biological phenomenon of protein aggregation is a major issue in therapeutic protein development, since the presence of these impurities reduces the potency of the drug formulation, even if non-toxic. Monoclonal antibodies must be free from these aggregate impurities.”

And size-exclusion chromatography is a widely applied technique for protein characterization and quality control. The new columns feature high pore volume per unit column volume, low sample adsorption (due to the derivatization of the particle surface with ligands containing diol functional groups) and what Tosoh calls “excellent” column efficiency, all contributing to what it says is unsurpassed sample resolution.

“This newest line of UP-SW columns offers all the first-in-class qualities users have come to expect from TSKgel SEC SW columns, with the added advantage of the higher exclusion limit for analysis of high molecular weight proteins and impurities,” commented Philip Hoang, technical marketing specialist for analytical chromatography at Tosoh.

**Liquid-stable enzyme calibration verification**

PROVIDENCE, R.I.—Verichem Laboratories has announced the availability of a ready-to-use, liquid-stable product expressly designed for the calibration verification of any “wet” chemistry testing system. Specifically, the Enzyme ER Verifier Kit is a multi-analyte, six-level solution kit of liquid stable materials, comprised of nine separate clinical enzyme components and covering a total of 54 individual activities.

The enzyme components included in the kit are ALT, ALP, AST, cholinesterase, CK, GGT, LD and lipase. According to the company, “The availability of this unique kit is certain to address the need of a wide variety of medical laboratory professionals, including those involved with clinical testing, research applications, and in the development and manufacturing of in-vitro diagnostic products.”

The company says the new kit “represents the cutting edge in enzyme test calibration verification materials, as its proprietary formulation is specifically designed to include at least one set point for each enzyme in the normal range. Plus, the use of purified source components and liquid format eliminates matrix variations and reconstitution errors common with lyophilized or serum-based products. In addition, the material’s protein balance, pH and ionic content are constant across concentration levels for optimum linearity.”

Reportedly, the linear relation for the set is included in the product insert so the kit can be used for reportable range verification of any automated wet chemistry method. Plus, for added convenience, a separate value assignment sheet is included with targets for popular Abbott, Beckman Coulter and Roche Diagnostics clinical chemistry systems.

**Focused solutions for cell culture workflows**

WAYNE, N.J.—ProCulture, a new workflow-minded product line for cell culture from Bel-Art and Wilmad-LabGlass brands (and available through SP Scienceware), covers multiple steps of the cell culture process from isolation to harvesting. Products include an array of shaker flasks and spinner flasks with a unique impeller that is said to increase aeration and eliminate dead spots, as well as an orbital shaker platform that converts an existing magnetic stir plate into an orbital shaker at a fraction of the cost of an orbital shaker.

“The ProCulture line includes products that can simplify researchers’ cell culture experiments,” explained Kathleen Hanek, portfolio manager for SP Scienceware. “There are tried-and-true items such as shaker flasks and storage racks, as well as products you can’t find anywhere else.”

**CONNECT:**
COVID and cancer

Roswell Park to assess immunotherapy combination in cancer patients with COVID-19

BUFFALO, N.Y.—A unique two-drug immunotherapy combination first evaluated at Roswell Park Comprehensive Cancer Center as an approach for treating some cancers will soon be available to cancer patients with COVID-19 through a clinical trial at Roswell Park.

The U.S. FDA has authorized clinical researchers at the center to conduct a study assessing the safety and effectiveness of giving both rintatolimod and interferon alfa to cancer patients with COVID-19. The study is one of very few worldwide to repurpose an experimental cancer therapy as a treatment for COVID-19, notes Roswell Park.

“This is exciting and noteworthy science,” says Roswell Park President and CEO Dr. Candace S. Johnson. “It’s a rare example of a concept for a COVID-19 therapy that emerged from academic researchers rather than a pharmaceutical company, and it was a Roswell Park team that looked at the way these two drugs work and saw a possibility for them to enhance each other’s effects.”

Dr. Pawel Kalinski, vice chair for translational research at Roswell Park, was the first researcher to propose giving these two immune-modulating drugs in combination as treatment for cancer. Kalinski is scientific lead on five clinical studies in progress or in development assessing the combination in patients with solid-tumor cancers, including breast and colorectal cancer. He and clinical principal investigator Dr. Brahm Segal will lead the team that will evaluate whether the two drugs may function effectively together as antiviral agents that could benefit patients with COVID-19.

“There are similarities between cancer and COVID-19, which both manage to avoid activating the interferon pathway,” said Kalinski, who will be scientific lead on the study. “This helps them to go undetected and spread in patients’ bodies, and differentiates them from viruses that cause the common cold, which cause rapid symptoms and are rapidly cleared by the immune system.”

“We believe that the two agents to be tested in our trial, given together, can activate the missing interferon response in COVID-19-infected cells,” he added. “This would induce protective interferons and other antiviral factors in adjacent cells, stopping the virus from spreading in patients’ bodies and generating a synergistic effect that could help cancer patients with mild or moderate COVID-19 to fight the virus before it causes serious damage to the lungs or other organs.”

Patients with cancer and COVID-19 have a risk of severe illness up to five times higher than people without cancer, underscoring the importance of work to develop new treatment options, according to Roswell Park.

The new clinical trial will test the safety of the combination regimen in patients with cancer and mild to moderate COVID-19, and the extent to which this therapy will promote clearance of the SARS-CoV-2 virus from the upper airway. Earlier published research from Kalinski’s lab has demonstrated that the combination of rintatolimod and interferon alfa-2b shows synergistic activity in preclinical cancer treatment models.

The Phase 1/2b study will enroll approximately 40 patients in two stages. Phase 1 will see 12-24 patients receiving both rintatolimod and interferon alfa-2b at escalating doses. Once that initial phase is complete, further study participants will be randomized to one of two arms: one receiving the two-drug combination and a control group who will not receive rintatolimod or interferon alfa but will receive best available care.

AIM ImmunoTech has agreed to provide rintatolimod (Ampligen) at no charge for this study.
Paired AAV vectors and AI
Dyno Therapeutics emerges from stealth mode with collaborations in eye and muscle disease

CAMBRIDGE, Mass.—May 11 saw Dyno Therapeutics officially launch as a company from stealth mode and announce two strategic collaborations with Novartis and Sarepta Therapeutics to develop improved gene therapies with adeno-associated virus (AAV) vectors based on artificial intelligence (AI) technology. Dyno could potentially receive more than $2 billion in payments under these collaboration agreements. Dyno applies AI with its proprietary machine learning platform, CapsidMap, to discover novel AAV vectors with delivery properties that are said to significantly improve upon current approaches to gene therapy and expand the range of diseases treatable with gene therapies.

The Novartis deal involves research, development, and commercialization of gene therapies for ocular diseases. The partnership will allow the parties to utilize CapsidMap along with Novartis’ expertise in gene therapy development and global commercialization.

“Many eye diseases are ideally suited to being treated with gene therapies, and more opportunities can be opened with new and improved AAV vectors. With their extensive ophthalmologic expertise, Novartis is an ideal partner to leverage Dyno’s platform to design AI-powered vectors to expand the impact of gene therapies for ocular diseases,” commented Dr. Eric D. Kelsic, CEO and co-founder of Dyno Therapeutics.

“Many eye diseases are ideally suited to being treated with gene therapies, and more opportunities can be opened with new and improved AAV vectors. With their extensive ophthalmologic expertise, Novartis is an ideal partner to leverage Dyno’s platform to design AI-powered vectors to expand the impact of gene therapies for ocular diseases,” commented Dr. Eric D. Kelsic, CEO and co-founder of Dyno Therapeutics.

An additional $20M for Ebola Sudan and Marburg vaccines

WASHINGTON, D.C. & ROME—The Sabin Vaccine Institute and its partner ReiThera Srl have announced that the Biomedical Advanced Research and Development Authority (BARDA), part of the U.S. Department of Health and Human Services, has exercised the first two options—valued at $20 million—under the BARDA award to advance the development of vaccines against Ebola Sudan and Marburg viruses through Phase 2 clinical trials. In September 2019, BARDA awarded Sabin a development platform contract valued at $128 million, and now has provided the initial funding award of $20.5 million to enable the manufacture and release of clinical vaccine material developed by ReiThera, a specialist in the development and GMP manufacturing of adeno-vector vaccines. The funding will also support nonclinical studies to evaluate efficacy and immune response.

“Ebola Sudan and Marburg are among the world’s deadliest viruses, causing hemorrhagic fever with subsequent death in an average of 50 percent of cases. A closely related strain, Ebola Zaire, has caused more than 2,200 deaths since 2018 in the Democratic Republic of Congo. “As the world has begun to appreciate, the next deadly outbreak is not a question of if, but when. At a time when global health and security are under siege by the novel coronavirus, we are grateful for BARDA’s foresight in funding programs like ours that will help guard against future pandemics,” said Sabin CEO Amy Finan. “We also greatly value ReiThera’s partnership, given their extensive experience in vaccine manufacturing and the development and GMP manufacturing of adeno-vector vaccines.”

Under a 2019 agreement between GlaxoSmithKline (GSK) and Sabin, Sabin exclusively licensed the technology for the proprietary ChAd3 platform, and acquired certain patent rights specific to these vaccines.

This new funding from BARDA will enable Sabin and ReiThera to advance the investigational Ebola Sudan and Marburg vaccines through GMP manufacturing and release of ChAd3-MARV and ChAd3-SUDV Phase 2 clinical material. A second funding option of around $20 million will support efforts to conduct pilot efficacy and immunogenicity studies. Additional nonclinical studies, as well as Phase 2 clinical trials in the United States and Africa, may be supported by an additional $87.5 million under this contract.

A universal antiviral to protect elderly adults from COVID-19

PHOENIX & JERUSALEM—Mirror Biologics Inc. and the Hadassah- Hebrew University Medical Center’s Center for Immunotherapy and Immunobiology Research have announced the publication of a manuscript in the Journal of Translational Medicine describing the scientific rationale for a new approach for vaccine development for the elderly. Mirror Biologics is the commercial development arm of Israel-based Immunobiological Therapies Ltd.

The new approach uses a patent-pending technology called AlloPrim, which is designed so that a series of injections of bioengineered cells, called AlloStim, could provide protection from any future viral infection—including COVID-19, influenza and future mutations of these viruses or an outbreak of a new novel virus. The idea behind the technology is to prime the elderly immune system to respond in the same manner as a healthy, younger immune system would respond.

“The novel mechanism described in the manuscript has the potential to become an important new tool in our fight against the current pandemic and preparedness against any future pandemic,” said Francesco M. Marincola, editor-in-chief of the journal.

“This technology is especially unique in that it targets modification of the elderly immune system, which tends to respond poorly to immunotherapy and vaccines.”

New tool for coronavirus-specific intestinal cell research

CAMBRIDGE, U.K.—Induced pluripotent stem cell (iPSC) biologics company DefiGEN says it has identified iPSC-derived intestinal organoids that could be used to help structure in-vitro studies of the biology of SARS-CoV-2 infection across cohorts of multiple patients.

While SARS-CoV-2 primarily targets the respiratory system, studies have shown that it also infects and multiplies within the intestinal epithelium. iPSC-derived organoids exhibit characteristics that closely mimic the in-vivo intestinal epithelium, making them a valuable surrogate model for studying the virus.

According to the company, several studies have proven that angiogenesis-inhibiting enzyme 2 (ACE2) expression in host cells is required for SARS-CoV-2 recognition and infection. Activity of membrane protease TMPRSS2, which is released by the coronavirus’ Spike protein and facilitates the membrane fusion with the host cell. The human intestine is one of the few human tissues with high ACE2 and TMPRSS2, and therefore is a good candidate to study COVID-19 and the mechanisms of SARS-CoV-2 infection.
Covering the News of Pharma, Biotech & Life Science

YOUR REGULAR DOSAGE OF NEWS IN THE AREAS OF:

- DISCOVERY
- RESEARCH & DEVELOPMENT
- PRECLINICAL
- CLINICAL TRIALS
- DIAGNOSTICS
- CONTRACT SERVICES
- BUSINESS & GOVERNMENT POLICY

For the pharma, biotech and life-sciences professional, understanding the complex process that results in new marketed therapeutics is an on-going challenge. In DDNews, you get insightful reporting and analysis of each stage in the pipeline—in print and online—from a staff of experienced life-science journalists. It’s an information resource you can’t find anywhere else.

Are there important issues, research areas or technologies you would like to read more about in DDNews?

Let us know at twitter (@DDNewsOnline) or friend us on Facebook.