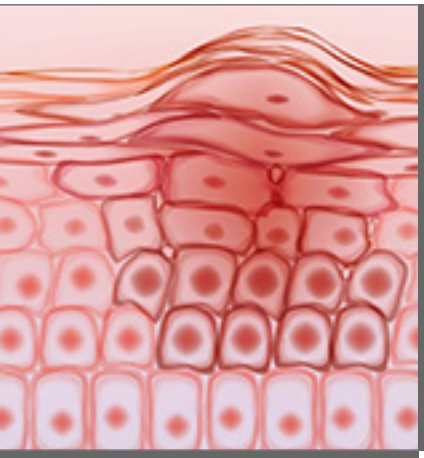
BioWorld

The news source of record covering the development of innovative human therapies
Actionable Intelligence • Incisive Analysis

Clarivate Analytics

December 17, 2018
Volume 29, No. 243



Toll bridge: Idera phase II results could presage win in later-stage combo trial

By Randy Osborne, Staff Writer

Wall Street didn't seem much enthused about Idera Pharmaceuticals Inc.'s data from the ongoing phase II trial called Illuminate-204 testing the intratumorally delivered Toll-like receptor 9 (TLR9) agonist tilsotolimod in combination with Yervoy (ipilimumab, Bristol-Myers Squibb Co.) against melanoma, but lead investigator Adi Diab from MD Anderson Cancer Center said that "to see such a durable response for these patients really creates hope. This is clearly an effective combination."

See Idera, page 3

Innovent's Avastin biosimilar clears hurdle in China trials

By Elise Mak, Staff Writer

HONG KONG – HKEX-listed Innovent Biologics Inc. said its IBI-305 referencing Roche Holding AG's Avastin (bevacizumab) has met primary endpoints in two randomized, head-to-head trials, putting the company one step closer to bringing to market one of the first Avastin biosimilars approved in China.

An injectable drug candidate, IBI-305 is a recombinant humanized anti-VEGF monoclonal antibody to treat EGFR-TKI failure non-small-cell lung cancer (NSCLC) and hepatocellular carcinoma (HCC).

"The results of the trials have shown a high similarity between IBI-305 and Avastin," Michael Yu, Innovent's CEO, told *BioWorld*. "The next step is to file an NDA with China's National Medical Products Administration [NMPA, formerly the CFDA] in the first quarter of 2019."

Currently, Innovent is tight-lipped about the details, but Yu revealed that the company will disclose more at an

See Innovent, page 4

Genesis Conference 2018

When health care meets tech: Panelists offer advice for building blended syndicates

By Nuala Moran, Staff Writer

LONDON – The rise of digital health and the application of artificial intelligence and big data, to preserves such as drug discovery, real-world patient monitoring and the analysis of medical images, is forcing investors in traditional life sciences startups out of their comfort zone and propelling them to form syndicates with tech venture capitalists.

There is significant market pull from health care providers drowning in the sea of rising

See Genesis, page 5

DoJ memos seen as having modest impact on federal prosecutors

By Mark McCarty, Regulatory Editor

WASHINGTON – Several memos directed toward U.S. federal prosecutors have surfaced during the current year, including one that spells out a seemingly novel policy regarding whistleblower lawsuits. A panel at a meeting of the Food and Drug Law Institute indicated that while the defense bar sees those memos as hopeful signs, the memos largely reflect the mainstream of federal prosecutor practice rather than represent a sea change in policy, leaving life sciences companies with more or less the same set of legal hazards as existed before 2018.

See FDLI, page 7

The BioWorld Biome

Frankenseeds

Amyloid beta seeds have decades-long staying power

By Nuala Moran, Staff Writer

LONDON – Vials of cadaver-derived human growth hormone in storage for more than 30 years were contaminated with amyloid beta seeds that promoted development of Alzheimer's-related amyloid beta pathology in mice.

The finding supports the hypothesis that amyloid beta pathology can be transmitted to humans by iatrogenic means. It also adds to evidence from cellular and animal models that the propagation and spread of prion-like misfolded host proteins

See Amyloid beta, page 6

Newco News

Validated ECM platform helps Engitix draw series A round to expand into drug development

By Nuala Moran, Staff Writer

LONDON – Engitix Ltd. has raised £5 million (US$6.4 million) in a series A to flip the business model from drug discovery services to drug development and to finance preclinical testing

See Engitix, page 8

Bench Press

BioWorld Senior Science Editor Anette Breindl takes a closer look at translational medicine

Read this week's edition

Other news to note

Advaxis Inc., of Princeton, N.J., disclosed in an 8-K filing that on Dec. 10, it received a written notice of termination from **Amgen Inc.**, of Thousand Oaks, Calif., with respect to the license and collaboration deal inked in 2016 for Advaxis' ADXS-NEO preclinical immunotherapy program using the *Listeria monocytogenes* attenuated bacterial vector. The termination is effective Feb. 8, 2019. ADXS-NEO is in clinical development, and Advaxis said it will evaluate whether to repartner the program. Shares of Advaxis (NASDAQ:ADXS) fell 14 cents, or 37 percent, to close Friday at 24 cents. (See *BioWorld Today*, Aug. 3, 2016.)

Axovant Sciences Ltd., of Basel, Switzerland, said it licensed exclusive worldwide rights for the development and commercialization of two gene therapy programs to address GM1 gangliosidosis and GM2 gangliosidosis (also known as Tay-Sachs and Sandhoff diseases) from the University of Massachusetts (UMass) Medical School. The therapies, AXO-AAV-GM1 and AXO-AAV-GM2, are each designed to introduce functional copies of the respective genes encoding the critical enzymes impacted in those diseases, with an aim to improve survival and enable children to reach key developmental milestones. In prior animal studies conducted with the gene therapies, dose-dependent increases in enzyme activity, reductions in accumulated gangliosides and prolonged survival have been observed. Under the terms, Axovant will make payments to UMass Medical School tied to development, regulatory and commercial milestones. Specific terms were not disclosed.

Bioarctic AB, of Stockholm, said partner **Abbvie Inc.**, of North Chicago, received U.S. Federal Trade Commission clearance to license Bioarctic's alpha-synuclein antibody portfolio for Parkinson's disease and other potential indications. (See *BioWorld*, Nov. 5, 2018.)

Boehringer Ingelheim GmbH, of Ingelheim, Germany, disclosed first interim results from the ongoing, non-interventional VARGADO study using Vargatef (nintedanib) and docetaxel in routine clinical practice in patients with stage III/IV locally advanced or metastatic non-small-cell lung cancer of adenocarcinoma histology. Despite a limited sample size, data add to the body of evidence for nintedanib in lung adenocarcinoma following pre-treatment with chemotherapy and immune checkpoint inhibitor therapy, the company said. Data were presented at the ESMO Immuno-Oncology Congress in Geneva.

Grünenthal GmbH, of Aachen, Germany, and **Ondosis AB**, of Gothenburg, Sweden, said they entered an exclusive collaboration to develop Ondosis' technology for prescription medicines in all pain-related indications. The agreement also entails an option for Grünenthal to an exclusive worldwide license to the technology in those indications. The handheld device enables individualized dosing of oral medicines in micro units. Under the terms, Ondosis will receive a technology access fee in addition to later development and regulatory milestone payments, as well as sales-related royalties. Financial terms were not disclosed.

Neem Biotech Ltd., of Cardiff, U.K., together with the Welsh Wound Innovation Centre and Sheffield Collaboratorium for Antimicrobial Resistance and Biofilms, received a £50,000 (US$62,851) inaugural National Biofilms Innovation Centre Proof of Concept grant. It will be used to expand the development and testing of effective antibiofilm interventions, specifically to expand data on the biological activity of Neem's candidate compounds for managing bacterial infections in wounds.

BioWorld

BioWorld (ISSN# 1541-0595) is published every business day by Clarivate Analytics.

Opinions expressed are not necessarily those of this publication. Mention of products or services does not constitute endorsement.

Our newsroom

Lynn Yoffee (News Director), Jennifer Boggs (Managing Editor), Peter Winter (*BioWorld Insight* Editor), Marie Powers (News Editor), Anette Breindl (Senior Science Editor), Mari Serebrov (Regulatory Editor), Amanda Lanier (Managing Editor), Karen Pihl-Carey (Analyst), Ann Marie Griffith (Production Editor)

Staff writers: Michael Fitzhugh, Randy Osborne, Shannon Ellis, John Fox, Nuala Moran, Brian Orelli, Alfred Romann, Tamra Sami, Cormac Sheridan

Practical information

For Sales Inquiries: http://clarivate.com/life-sciences/news/bioworld/. NORTH AMERICA, Tel: +1-855-260-5607. Outside of the U.S. and Canada, Tel. +44-203-684-1797. For Customer Service Inquiries, NORTH AMERICA, Tel: +1-800-336-4474. Outside of the U.S. and Canada, Tel. +44-203-684-1796.

For ad rates & information, please contact Anthony Quagliata at (929) 454-2936, or email anthony.quagliata@clarivate.com .

For photocopy rights or reprints, please contact Anthony Quagliata at (929) 454-2936, or email anthony.quagliata@clarivate.com .

Send all press releases and related information to newsdesk@bioworld.com.

Business office

John Borgman (Director of Commercial Competitive Intelligence), Donald Johnston (Senior Marketing Communication Director, Life Sciences)

Contact us

Jennifer Boggs, (770) 880-3631 | John Borgman, (831) 462 2510 | Anette Breindl, (770) 810-3134 | Michael Fitzhugh, (770) 810-3064 | Donald Johnston, (678) 641-0970 | Nuala Moran, 44-7778-868-579 | Randy Osborne, (770) 810-3139 | Marie Powers, (770) 810-3136 | Mari Serebrov, (770) 810-3141 | Cormac Sheridan, 353-87-6864323 | Peter Winter, (770) 810-3142 | Lynn Yoffee, (434) 964-4011

Idera

Continued from page 1

Shares of Exton, Pa.-based Idera (NASDAQ:IDRA) closed Friday at $3.98, down $2.62, or 39.7 percent, after the company shared data from the study that tested the combo for unresectable or metastatic melanoma after the failure of PD-1 inhibitor therapy. Altogether, 32.4 percent of patients evaluable for efficacy achieved partial response or better and 76.5 percent achieved disease control. Tumor shrinkage was seen in injected as well as uninjected lesions, suggesting an abscopal effect. Injections with tilsotolimod are designed to selectively enable the T cells to recognize and attack cancers that remained elusive and unrecognized by the immune system exposed to checkpoint inhibitors alone, while limiting toxicity or impact on healthy cells.

Thirty-seven patients given 8 mg of tilsotolimod in combination with ipilimumab, an immune checkpoint inhibitor targeting CTLA-4, were evaluated for the update. Of those, 34 patients were evaluable for efficacy and all for safety. Accrual continues, with four more patients dosed. Responses, including two complete responses (CRs) turned up in 11 patients. Duration of response ranges from more than one month to more than 30 months, with 36 percent of responses ongoing.

Cancer is a disease of growth and spreading, Diab reminded investors during a conference call on the latest data. "When you strip those two features from the cancer, no growth and no new lesions, this is a win," he said. "Of course, these patients do have cancer but they don't have the spread and growth, and that translates into overall survival [OS] most of the time and improved quality of life. I want to emphasize that the other name of 'disease control rate' is 'clinical benefit rate' – that's really what it means."

Per RECIST v1.1 criteria, the overall response rate (ORR) totaled 29.4 percent; one patient with an unconfirmed partial response (PR) at the end of treatment assessment progressed due to a new lesion at the three-month follow-up assessment. Twenty-six of the 34 evaluable patients showed disease control (CR, PR, or stable disease). Responding subjects included one with mucosal melanoma and one patient with acral melanoma, two forms that are especially hard to treat. Two of five enrollees with prior ipilimumab experience achieved responses, and the pairing continued to be generally well-tolerated. Nine of 37 subjects (24.3 percent) had immune-related toxicities, indicating that the duo doesn't appear to add immune-related hitches as compared to ipilimumab by itself. Injection-related toxicities were grade 1-2 transient fever and flu-like symptoms lasting less than 48 hours. The results show tilsotolimod is "synergizing with a checkpoint inhibitor and doing what it's supposed to do by means of activating the dendritic cells and the macrophages and creating a better tumor microenvironment," Diab said.

A RECIST v1.1 partial response of more than 2.5 years is ongoing in one patient treated with tilsotolimod 4 mg in combination with ipilimumab, the company said, and a RECIST v1.1 CR of more than a year is ongoing in a patient treated with tilsotolimod 16 mg in combination with Keytruda (pembrolizumab, Merck & Co. Inc.). The study is designed for patients with metastatic melanoma for whom treatment with the likes of pembrolizumab and Opdivo (nivolumab, Bristol-Myers Squibb Co.) has failed. Multicenter and dual-armed, the phase I/II experiment is measuring the safety and efficacy of tilsotolimod when used with either of those drugs.

TLR9s rising stars?

Idera's chief medical officer, Joanna Horobin, said researchers have "definitely seen patients who at the first disease assessment or the second have stable disease. After that it rolled into a response, [which] can be after they've completed their active treatment."

She also discussed the phase III trial now enrolling. "In terms of the patient population, we amended the phase II protocol some time ago to make sure that the patients that have come into the protocol most recently are essentially the same as the patients that will go into phase III, so I think it is appropriate for people to read over from the phase II protocol to phase III." Regarding the statistical power, "all of that has been discussed with the agency" which agreed to the plan, she said.

Called Illuminate-301, the phase III study – testing the tilsotolimod/ipilimumab combo in anti-PD-1-refractory metastatic melanoma – is recruiting patients at more than 80 clinical trial sites in the U.S., Europe, Australia and Canada. The trial is expected to sign up about 300 patients and measure ORR and OS rates vs. ipilimumab alone.

Also in the TLR9 agonist space is Berkeley, Calif.-based Dynavax Technologies Corp. with SD-101. At the European Society for Medical Oncology meeting in October, the company offered phase Ib/II data on the compound used with pembrolizumab. In 47 advanced melanoma patients naïve to anti-PD-1 therapy who received the 2-mg dose, the ORR was 70 percent, an identical number to that previously reported at the American Society of Clinical Oncology meeting in June, but with a greater than 50 percent increase in number of patients. The six-month progression-free survival rate was 85 percent. Researchers saw responses in injected lesions and non-injected distant lesions, including visceral metastases in the liver and lung, and responses were independent of baseline PD-L1 expression. Adverse events were transient, mild to moderate flu-like symptoms. The ORR was 21.4 percent in 29 melanoma patients refractory or resistant to anti-PD-1 therapy who received the 8-mg dose, and 27.3 percent in 22 patients with head and neck squamous cell carcinoma who were naïve to anti-PD-1, given the 8-mg dose.

Privately held Checkmate Pharmaceuticals Inc., of Cambridge, Mass., has its TLR9 player, CMP-001, in a phase Ib multicenter, open-label study giving the drug intratumorally with pembrolizumab in subjects with advanced cutaneous melanoma who are either receiving pembrolizumab, or who have either progressed on an anti-PD-1/PD-L1 therapy, or have failed to respond to at least 12 weeks of therapy. The trial is being conducted in two phases: a dose-escalation part to identify the recommended phase II dose and schedule; and an expansion phase to further characterize the safety, pharmacodynamics and preliminary evidence of antitumor activity of the combo. ♦

Innovent

Continued from page 1

international conference in the first half of next year.

What is known so far is that IB-I305 has met the primary endpoint, which is objective response rate, in CIBI305A301, a phase III, multicenter, randomized, double-blinded, parallel, positive-controlled study in patients with advanced nonsquamous NSCLC. The study began in November 2016.

With 450 patients enrolled, the study compared the efficacy, safety and immunogenicity between IBI-305 and Avastin in combination with paclitaxel/carboplatin in first-line treatment. Randomized at a 1-to-1 ratio to two treatment arms, the patients received 15 mg/kg of both agents in combination with paclitaxel/carboplatin for six cycles, then maintained the dosage at 7.5 mg/kg.

According to Innovent's prospectus in October, the blinded analysis of the interim trial data show the safety profile of IBI-305 is consistent with the reported safety profile for Avastin.

Innovent has yet to disclose any results for the secondary endpoints, which are the overall survival time and progression-free survival.

IBI-305 also met the primary endpoint in a smaller pharmacokinetic study that has demonstrated bioequivalence between Avastin and the biosimilar. That study, known as CIBI305A201, is a randomized, double-blinded, parallel, positive-controlled single-dose trial in 100 healthy subjects that started in March 2017 in China. It aims to assess the pharmacokinetic profile, safety, tolerability and immunogenicity of a single 3-mg/kg dose of IBI-305 compared to Avastin in the patients.

"The primary endpoints of AUC0-inf [extrapolated total area under plasma curve to time infinity] and AUC0-t [area under the plasma concentration time curve], as well as Cmax [the peak serum concentration that a drug achieves in a test area of the body after drug administration], t½ [half-life], drug clearance and volume of distribution, were similar for IBI-305 and Avastin at a 3-mg/kg dose level," Innovent said in its prospectus.

The company added that for each of AUC0-inf and AUC0-t, the 90 percent confidence intervals for the ratio of IBI-305 to Avastin were fully contained within 80 percent to 125 percent. The result demonstrated bioequivalence between the biosimilar and Avastin. "The pharmacokinetic profile plots demonstrated substantial overlap for the profile of IBI-305 and Avastin out to 2,000 hours after a single dose administration in normal volunteers."

Innovent submitted an IND application for IBI-305 to the NMPA in December 2014, and the approval came in May 2016.

In October, the company also got IND clearance to test the combination of IBI-305 and its anti-PD-1 monoclonal antibody, IBI-308 (sintilimab), to treat NSCLC and HCC.

Fierce competition

Competition in the anti-VEGF area for treating NSCLC is fierce in China. To date, there are seven other Avastin biosimilars in phase III trials, and one drug candidate has reached the NDA submission stage. In August, the NMPA accepted an NDA from Jinan-based Qilu Pharmaceutical Co. Ltd. for its QL-1101 and put it under the priority review pathway in October.

"By the end of this year, the biosimilar to Avastin will be the first to be approved in China," predicted Andrew Yu, director at strategy consultancy Monitor Deloitte's China Life Science Practice. (See *BioWorld*, Oct. 10, 2018)

Other competitors in the race include Shanghai Henlius Biotech Inc.'s HLK-04, Genor Biopharma Co. Ltd.'s GB-222, Beijing Mabworks Biotech Co. Ltd.'s MIL-60, Luye Pharma Group Ltd.'s LY-01008, Jiangsu Hengrui Medicine Co. Ltd.'s BP-102, Tot Biopharm Co. Ltd.'s TAB-008 and Bio-Thera Solutions Ltd.'s BAT-1706.

Since 2015, Roche's Avastin has been approved in China as a first-line treatment of advanced metastatic nonsquamous NSCLC, after it was first allowed in the country to treat metastatic colon and rectal cancers in 2010.

The China sales of Avastin were ¥1.7 billion (US$246.4 million) in 2017 and are expected to reach ¥8.8 billion in 2022 and ¥16.6 billion in 2030.

On Dec. 14, Innovent's shares (HKG:1801) fell 1.9 percent to HK$20.95 (US$2.68). Innovent remains the only Hong Kong-listed pre-profit biotech that is holding above its IPO price. (See *BioWorld*, Nov. 1, 2018.) ♦

Other news to note

Orchard Therapeutics Ltd., of London, and **Sirion Biotech GmbH**, of Martinsried, Germany, entered a license agreement in which Orchard licensed Sirion's Lentiboost technology to enhance manufacturing efficiency for certain of Orchard's ex vivo autologous hematopoietic stem cell gene therapy drug candidates. Under the terms, Sirion will be entitled to up-front and milestone payments and is eligible to receive royalties on net sales of future products that use its technology.

Prestige Biopharma Pte Ltd., of Singapore, said it reached a licensing agreement with **Cipla Ltd.**, of Mumbai, for its trastuzumab biosimilar, HD-201, under which Cipla will have exclusive rights to distribute and market the drug in selected emerging markets. Financial terms were not disclosed. HD-201 is a biosimilar to Herceptin (Roche Holding AG), used to treat patients with HER2-overexpressing breast cancer and HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma. It is in phase III development, with filings expected in the U.S. and Europe in 2019.

The U.S. Institute for Clinical and Economic Review (ICER) said it plans to assess the comparative clinical effectiveness and value of treatments for Duchenne muscular dystrophy (DMD). The report will be reviewed during a public meeting of the New England Comparative Effectiveness Public Advisory Council in July 2019. The assessment will focus on two drugs from **Sarepta Therapeutics Inc.**, of Cambridge, Mass.: Exondys 51 (eteplirsen), which gained FDA approval in September 2016, and golodirsen, which has an anticipated PDUFA date in mid-2019. A draft scoping document, which will provide more detail on ICER's planned analysis, will be available on Jan. 11, 2019. That document will be open to public comment for three weeks.

Genesis

Continued from page 1

costs. As a result, "the opportunities are too attractive to ignore," said Rowan Gardner, veteran angel investor and chair of Biolauncher Ltd., a company specializing in providing services to life sciences startups, opening a panel debate: "Is convergence driving new investment syndicates?" at the Genesis conference in London.

If the opportunity is evident, there are hurdles to navigate, such as finding tech investors with the right experience, getting access to suitable deal flows, adjusting to different cultures and product life cycles, and agreeing on commercialization strategies.

"There is a need to change behaviors in building syndicates around converging technologies," Gardner said.

David Holbrook, physician and partner at Lifearc, the VC arm of the U.K. Medical Research Council, agreed. "You cannot ignore this. The cozy world we all know is going to change and the change is going to be profound."

There have been waves of convergence in the past, for example, materials science meeting biology in the development of novel biomaterials. But there has been nothing on the scale of the tech and health care convergence.

"Like, I suspect, many in the audience, I've been to a number of presentations by leaders of the IT industry this year. They are terrifying," Holbrook said.

Digital health stands at the confluence of four huge forces. First, the incredible rise in capacity and parallel fall in cost, of computer processing power and data storage. Those resources are now available at hourly rates, with no need to sink huge amounts of capital into your own infrastructure, Holbrook noted.

The second is the massive amount of data that processing power is generating. "It's almost too much for the scientists to elucidate," said Holbrook.

And now, rather than being stuck in corporate silos, much of those data – at the owner's discretion – are shareable.

Those three forces are ranged in front of what Holbrook described as "a massively hungry marketplace" of providers worldwide who are desperate to constrain the rising costs of health care. "This is unparalleled. Nothing before has every looked like this," Holbrook told delegates.

A different mindset

All of which presents investors whose experience is based on the highly regulated, snail's pace of life sciences startups with a big learning curve. Dan Mahony, fund manager at the public markets investment group Polar Capital Global Health Trust plc, suggested it is important to be looking at implementation and commercialization from the point of pulling a syndicate together.

The mindset has to be different, said Mahony. The market is looking for products with commercial traction. "That is a far more important consideration in digital health than when you are developing a drug," he said.

> *"You cannot ignore this. The cozy world we all know is going to change and the change is going to be profound.*
>
> David Holbrook,
> Partner at Lifearc, the VC arm of the U.K. Medical Research Council

The thought resonated with Aitua Ekhaese, of North Hill Advisory Partners, which advises family officers and non-expert institutional backers. "You need to identify the discrete parts and see them as a whole. Don't get overexcited by science – you've got to think about getting to market," he said.

Rather than being in control of the whole path from startup to market, it is necessary to join up the dots. "It's an interconnected industry; the job is a lot harder," Ekhaese said.

That all rings true for Diane Lejeune, senior investment manager at PMV, a Belgian VC that invests in seed and series A rounds. "We are an early investor, but we find we have to check the market pull much earlier on compared to with biotech [startups]," she said.

A further challenge in setting up combined tech/life science syndicates is the change of expertise around the boardroom table.

"Here we are all out of our comfort zones; all coming from different angles of engineering, marketing and science," Lejeune said. "You need to be able to attract different types of people and skills and give the right weight to each of these different voices."

Eric Elenko, chief of research and strategy at London-quoted technology commercialization company Puretech Health plc, agreed it can be difficult to blend a harmonious whole from different disciplines, each of which has different perspectives and culture, to create something new.

The approach at Puretech is to identify a common problem or mission that engenders a common frame of reference for everyone. All elements selected to address a problem have to be the best. "It has to be the best biology and the best software, and there has to be a willingness to collaborate and learn," Elenko said.

A convergence landscape

If those are some of the ingredients as individual investors see it, that still begs the question of how to put a consortium together.

Gardner suggested it is helpful to look to the basics, such as searching for partners who will make your capital go further, and who will give you access to better deal flow.

"In the convergence landscape, building out syndicates to bring the skills to the table is a really important consideration," Gardner said.

Traditional life sciences investors moving into digital health

See Genesis, page 9

Amyloid beta

Continued from page 1

play a role in the pathogenesis of Alzheimer's and Parkinson's diseases, amyotrophic lateral sclerosis (ALS) and other neurodegenerative disorders.

The research published in *Nature*, has implications for both the prevention and treatment of Alzheimer's disease (AD), and should prompt a review of possible transmission of amyloid beta seeds by medical and surgical procedures, which have long been recognized as posing a risk of accidental prion transmission, according to lead author John Collinge, of University College London's (UCL) Institute of Prion Diseases.

"It presents a new way of thinking about [AD]," Collinge said. "My background is in prion diseases, which are either sporadic, or inherited, or acquired from environmental exposure. It was thought Creutzfeldt-Jakob disease [CJD] was unique in that respect. But not now."

Commenting on the research, Bart De Strooper, director of the UK Dementia Research Institute at UCL, said, "It adds to the ongoing discussion of similarities between the pathogenic mechanisms in prion diseases and other neurodegenerative disorders, in particular Alzheimer's and Parkinson's diseases, [which] are characterized by abnormally folded proteins that spread through the brain and cause dementia."

From CJD to AD

The trail of evidence goes back to 1985. Until then, children with growth deficiencies were treated with human growth hormone from donated pituitary glands, a practice that was ended when it was discovered the product could contain the prion protein that causes CJD.

More than 200 individuals worldwide treated with donated human growth hormone are known to have died of CJD. In the U.K., 80 of 1,883 patients receiving the product had developed the neurodegenerative disease as of July 2018. New cases are still being diagnosed.

It was in conducting autopsies of eight of those patients, ages 36 to 51, that evidence of amyloid beta pathology was found. The amount of aggregated protein was out of proportion to what would be expected in people that young, Collinge noted.

Reporting those findings in September 2015, Collinge and colleagues concluded that in addition to CJD prions, the growth hormone was possibly contaminated with amyloid beta seeds.

Collinge suggested further research was necessary to confirm that and, happily for him, Public Health England has maintained an archive of vials of donated human growth hormone from batches to which the eight patients were exposed.

That enabled the researchers to confirm biochemically the presence of both amyloid beta and tau proteins in vials of growth hormone prepared by one particular method. Vials purified by three other methods were not contaminated in that way.

Although they can be shown to be present, Collinge said the precise structure and nature of those amyloid beta and tau seeds is not understood. "We think they are assemblies of a-beta peptides but their molecular structure is at present unknown," he told *BioWorld*.

> *"We know that Alzheimer's is a complex disease; this paper suggests it is more complex than we thought.*
>
> Roger Morris
> King's College London

To determine if the contaminated batches have amyloid beta seeding activity, the suspect growth hormone was administered to mice that were genetically engineered to express a humanized version of Alzheimer precursor protein. "The human peptide [would] interact with the human [amyloid beta] seeds, assuming they were in the material injected," said Collinge.

In order to optimize the chance of detecting seeding activity in the scarce amount of material that was available, the growth hormone was injected directly into the brain.

At 240 days post-injection, amyloid beta deposits and cerebral amyloid angiopathy (CAA), an Alzheimer's-related condition in which amyloid gathers around the outside of blood vessels in and around the brain, were found in mice that received the contaminated growth hormone. There was no sign of similar pathology in a number of different controls, including in mice that received the currently used recombinant hormone.

The degree of CAA and the amount of cerebellar amyloid beta deposition in mice inoculated with donated growth hormone were far less pronounced than when the engineered mice were injected with brain homogenates from patients who died from Alzheimer's disease.

However, the researchers said, "It is remarkable that detectable seeding activity has persisted at all, after decades of storage." That is perhaps all the more remarkable, given the vials were stored at ambient temperatures.

"It fits with the hypothesis, but I have to say, I was amazed to see it in a dry powder that had sat around for 30 to 40 years," Collinge told a teleconference held to discuss the research. "It is clear CAA is transmissible and it is a key precursor of Alzheimer's disease. The mice didn't develop Alzheimer's disease because they don't get it," he said.

Collinge is now planning further studies in tau-expressing mice to see if human growth hormone in the vials also can seed aggregation of that protein.

Although the eight patients died of CJD, it is likely if they lived longer, seven of them would have developed Alzheimer's, according to the researchers. And, they added, it is important to emphasize that the seeded amyloid beta deposition is not benign, as evidenced by the fact that several of the patients had CAA, a disease that is caused by amyloid beta deposition.

See Amyloid beta, page 9

FDLI

Continued from page 1

The session addressed three communiqués coming out of the U.S. Department of Justice in 2018, including the Granston memo for dismissal of qui tam lawsuits, and the Brand memo for limiting the use of deviations from federal agency guidance as demonstrations of violations of the law. Also on tap was the policy declaration by Deputy Attorney General Rod Rosenstein regarding "piling on," which addresses the need to coordinate prosecution of defendants across federal agencies so as to avoid imposing penalties upon the defendant organization that are disproportionate to the underlying criminal or civil offense.

All three of those policies have been hailed at one point or another as a tectonic shift in how federal prosecutors go about dealing with prosecutions under the False Claims Act and other federal laws, but the panelists at a session dealing with enforcement trends said those policies, to some extent, follow rather than lead prosecutor practice, thus taking some of the cheer out of the defense bar's enthusiasm.

DoJ's Eyler says 'vigorous support'

Moderator Michael Blume, a partner at Venable LLP, said there are reports that the current White House has been less enthusiastic about enforcement generally than its predecessors, although Gustav Eyler, acting director of the consumer protection office at DoJ, seemed to differ. "We have outstanding and vigorous support for what our branches are doing," Eyler said, adding, "We have seen our resources and authorities bolstered" under the Trump administration.

Michele Sartori, a partner at Hogan Lovells LLP, said that despite the news about the memos, "this is not the time to sit back and relax" where compliance is concerned. Sartori said the Granston and Brand memos offer the defense bar another set of tools to argue on behalf of clients, adding that the Rosenstein policy – Rosenstein pointedly indicated he preferred that the policy not be referred to as the Rosenstein memo – "may have an impact and be used to curtail actions that shouldn't go forward." However, Sartori said she is hoping for more clarity from DoJ on those points.

Lisa Dwyer, a partner at King & Spalding LLP, made reference to the Feb. 28 public address by Deputy Assistant Attorney General Ethan Davis regarding off-label promotions. Dwyer said Davis had indicated that DoJ won't act on claims unless those claims are determined to be false or misleading, or otherwise raise significant public health concerns. That is consistent with statements by other officials with the department, Dwyer said, adding, "I don't think it has given any of us in this room carte blanche" to promote products off-label with no regard for the law.

Dwyer said, "I visualize off-label speech as a fried egg," explaining that agency guidances are the yolk, while the First Amendment "forms the boundary of the egg white." Low-risk speech is in the yolk, and the legal hazards elevate the farther into the egg white the speech strays. "Different people may see your speech differently," she said, however, suggesting that drug- and device makers tread carefully as they cannot count on any uniformity where commercial speech prosecutions are concerned.

Enforcement seen as a Rorschach test

The Rosenstein memo on piling on was well-received, Dwyer said, because a warning letter or DoJ action could trigger action on the part of state attorneys general, the result of which could be consent decrees that deny the company regulatory certainty. Dwyer pointed to the December 2017 consent decree between the state of Oregon and Dublin-based Medtronic plc as an example, a $12 million action undertaken in connection with the firm's promotion of the Infuse bone morphogenic protein device. That action followed the well-known coverage of Infuse in the June 2011 issue of *The Spine Journal*. Dwyer said any federal prosecution or litigation can serve as "a bit of a Rorschach test" for state and federal prosecutors, stating that the FDA would apply a different set of principles to the underlying facts than did Oregon's attorney general, Ellen Rosenblum. Consequently, Medtronic was in essence dealing with two different sets of rules.

Eyler advised that the piling-on policy is not a bar against parallel proceedings, although he said the policy is "an important directive" that serves to remind federal attorneys they need to coordinate both within the department and with state regulators "to ensure that the end result is proportional and equitable." Such cooperation will allow federal prosecutors to "tailor our investigation so that we hopefully are gathering the information we need to get to the right outcome" without unduly burdening the target, Eyler said.

The well-known problem of data accumulation means life sciences companies have tons of information for federal attorneys to sift through, however, and Eyler said companies can curry favor with federal prosecutors if they explain how they archive information. Drug- and device makers may want to have a process in place to provide federal attorneys with the most relevant material, a practice he said can cut down on the number of requests and save both time and money for both parties.

FDA-DoJ split a concern

Dwyer noted that DoJ and the FDA don't always agree about how to approach an enforcement issue, adding that "the reason for that is both agencies are enormous operations and there is imperfect coordination" between the two. The fix for that problem may be transparent communication with each agency as to communications with the other agency, and she said there are times when it might pay to reach out to DoJ and make the case for why the FDA approach to enforcement might be more appropriate.

Sartori concurred, stating that "it's just a matter of bringing the parties together," because "ultimately, the agencies are going to have to work it out." Nonetheless, she said, "it doesn't help to try to play the sides against each other." ♦

Engitix

Continued from page 1

of novel drugs discovered with its extracellular matrix (ECM) technology.

The company has patented a mechanical method for rapidly decellularizing human liver and other tissues, leaving extracellular scaffolds that retain their normal 3D architecture and tissue-specific biochemical and biomechanical properties.

That provides a more relevant medium to screen drug compounds targeting fibrosis, which is an ECM-related disease. It also forms the basis of disease-specific cellular models and is a source of new drug targets.

"The traditional drug discovery process in fibrosis and solid tumors relies on artificial in vitro substrates and animal models," said Giuseppe Mazza, co-founder and CEO of London-based Engitix. "So far, these models have been shown to have limitations in providing efficient therapies."

In collaboration with a number of pharma and biotech partners, Engitix has validated the ECM platform in tests of the efficacy of drugs in development for treating liver fibrosis.

The company also has used human liver, pancreas and intestine ECM scaffolds to generate models of primary liver cancer and liver metastases, and pancreatic and colon cancers.

The models have been used by Engitix co-founder Massimo Pinzani, director of the institute for liver and digestive health at University College London, in research into the pathology of fibrosis and solid tumors that has thrown up novel drug targets.

"We can get better understanding on how processes are happening in normal versus pathological environments," Mazza said. "We now have some drug targets discovered using our unique platform, and these will form the basis of our own development programs," he told *BioWorld*.

The series A funding round, led by an unnamed private investor, enables Engitix to advance preclinical development of three programs in liver fibrosis, liver cancer and pancreatic cancer.

Engitix is not abandoning services altogether, with Mazza saying it is a way of getting paid to learn more about the potential of the ECM technology. "When you run a services company, you always say yes, because you need the revenues. Now we have the funding, we will focus on in-house programs but will develop [new ECM models] if a partner agrees to pay in full, and not just for a two-month contract," he said.

It is now planned to double R&D capacity, recruiting 10 scientists, and to open an office in Boston.

Although ECM is acellular, it is far from inert. Rather, it is a dynamic structure that is constantly remodeled to control tissue homeostasis. Changes in ECM composition and mutations in the genes that govern remodeling are associated with fibrosis and the growth of solid tumors.

The series A funding of Engitix follows publication last July of a paper in which Mazza, Pinzani and colleagues describe their novel method for producing cubes of acellular human liver scaffolds from donated livers that were unsuitable for transplantation.

While other researchers have pursued that goal, Mazza's breakthrough came in applying high shear stress to enhance the distribution of detergents within the tissue, whilst minimizing the length of time the ECM is exposed to the detergents.

Mazza pushed the technique from taking 16 days to partially decellularize the liver cubes to completely decellularizing them in three hours, whilst maintaining the protein composition and 3D architecture. The cubes can be frozen.

Engitix claims it is the first company in the world to have a standardized, reproducible method for producing tissue- and disease-specific ECM scaffolds.

Human liver cells grown in liver scaffolds show markedly different gene expression compared to standard 2D cultures; when cancer cells are put into the scaffold, they take on a more invasive phenotype than in standard cell cultures.

In addition to offering advantages over like-for-like 2D in vitro tests, Engitix's models also can answer questions that 3D liver organoids cannot, said Mazza. "Organoids are cool for epithelial cells, but you need experimental models of human ECM," he said. ♦

Regulatory front

The **United States-Mexico-Canada Agreement** (USMCA) has been signed by the chief executives of each of the participating nations, but it has not been ratified by the U.S. Senate despite the passage of two weeks since the ceremonial signing Nov. 30. The agreement, which would overwrite the North American Free Trade Agreement, includes a concession from Canada regarding biotech exclusivity, currently set at eight years but scheduled to increase to 10 years upon enactment. The agreement also forces Canada's patent office to offer patent term adjustment to account for "unreasonable" delays in the processing of patent applications. That would be invoked if five years pass between the date of the filing and the issuance of the patent, or if three years pass after the applicant requests examination of the application, whichever is later. That requirement would not be retroactive, however, and Canada would have 4.5 years after implementation of the agreement to put the requirement into force. Jim Greenwood, president and CEO of the Biotechnology Innovation Organization, said upon the signing of the agreement that USMCA "has effectively prioritized biotechnology innovation across North America" thanks to the provisions for intellectual property. Greenwood said the agreement "is a major step towards bringing Mexico and Canada closer to the standards that has made the United States the world leader in biotechnology innovation." Scott Whitaker, president and CEO of the Advanced Medical Technology Association, said USMCA "represents a significant step forward in terms of transparency, regulatory fairness and ensuring open access" to all three markets. Whitaker urged the U.S. Congress and the legislatures of Mexico and Canada "to approve the USMCA as expeditiously as possible." The U.S. Congress is not expected to address the agreement until 2019.

Genesis

Continued from page 5

know they must broaden their perspectives. That has to be through partnerships, because there is simply not enough time to develop the necessary skills organically, said Holbrook.

Lots of the products and services developed under the digital health umbrella will not be marketed by pharma or medical devices specialists, but by tech companies like Amazon. "You need to be able to capitalize on that, to know who is going to buy a product, who is going to deliver it to the patient," Holbrook said.

For Elenko, it is important to seek out partners that bring more than capital alone, for example, providing access to networks or expertise, and also to ensure they can put in money beyond startup and series A rounds.

Convergence is changing syndication, Elenko said. "Tech is interested in life science and vice versa. Pools of capital that wouldn't ordinarily talk to each other will – and that will lead to breakthroughs." ♦

Amyloid beta

Continued from page 6

Technically transmissible, but not contagious

Collinge reiterated the conclusion reached in 2015, that there is no suggestion Alzheimer's disease is contagious, or can be transmitted by blood transfusion.

However, he said, it is important to re-evaluate the risks of iatrogenic transmission of CJD and potentially of Alzheimer's disease, in particular on neurosurgical instruments.

Roger Morris, professor of molecular neurobiology at King's College London, said the research adds to a series of demonstrations that beta-amyloid is "transmissible," in the sense that it can promote the formation of additional amyloid.

That could be a mechanism by which amyloid spreads in blood vessels. "However, despite positively inducing amyloid production by the blood vessels, [the growth hormone] failed to induce it in neurons. We know that Alzheimer's is a complex disease; this paper suggests it is more complex than we thought," Morris said.

Tara Spires-Jones, program lead at the UK Dementia Research Institute at Edinburgh University, contested the conclusion that Alzheimer's disease could be accidentally transmitted by medical procedures. Despite injecting the growth hormone into the brain, which would not happen with humans, the mice only developed a very small amount of amyloid pathology along blood vessels, which "on its own, is not sufficient to cause Alzheimer's," Spires-Jones said.

David Brown, professor of biochemistry at Bath University was more scathing, saying Collinge's work had done "little more" than reproduce earlier findings that amyloid protein can aggregate in clumps. "[It] does not provide any evidence whatsoever that Alzheimer's disease can be transmitted," Brown said. ♦

Financings

Axovant Sciences Ltd., of Basel, Switzerland, said it priced its underwritten public offering of 30 million of its common shares at $1 each with gross proceeds expected to be approximately $30 million. The underwriters have been granted a 30-day option to purchase up to an additional 4.5 million shares on the same terms and conditions.

The Medicines Co., of Parsippany, N.J., said it priced its private offering of $150 million in convertible senior notes due 2024. The notes will bear interest at a rate of 3.5 percent per year, payable semi-annually. The company has granted the initial purchaser an option to purchase up to an additional $22.5 million of the notes. It estimates that the net proceeds will be approximately $144.9 million (or $166.8 million if the initial purchaser exercises its option to purchase additional notes in full), and the funds will be deployed to support its development of inclisiran and for general corporate purposes.

Santhera Pharmaceuticals Holding AG, of Pratteln, Switzerland, said it completed its ordinary capital increase with the placement of 3.13 million new shares by way of an accelerated book building and raised gross proceeds of CHF23.5 million (US$23.55 million). The company intends to use the CHF-equivalent of $20 million of the net proceeds to pay the cash component to Allschwil, Switzerland-based **Idorsia Ltd.** for the acquisition of the option for the exclusive sublicense relating to Rockville, Md.-based **Reveragen Biopharma Inc.**'s vamorolone, a steroid drug designed to reduce side effects and allow for longer-term Duchenne muscular dystrophy (DMD) treatment than is possible with current glucocorticoid therapy. After payment, Santhera will have completed the option acquisition and secured its exclusive sublicensing rights to the product, which is designed to preserve upper and lower limb strength and function in boys with DMD who are able to walk. It will complement Santhera's existing DMD treatment, idebenone, which is available in the U.S. and Europe on a compassionate use basis for preventing loss of respiratory function in boys who have lost the ability to walk. (See *BioWorld*, Nov. 26, 2018.)

Other news to note

Trevena Inc., of Chesterbrook, Pa., said data presented at the American College of Neuropsychopharmacology as part of its ongoing collaboration with the National Institute on Drug Abuse showed TRV-743 reduced drug-seeking behavior in a rat model of relapse, suggesting it might be an oral maintenance treatment for addiction to opioids or heroin. TRV-734 is designed to target the same mechanism of action as Trevena's intravenous oliceridine, which selectively stimulates G-protein coupling at the mu-opioid receptor with low beta-arrestin recruitment.

Clinical data for Dec. 14, 2018

Company	Product	Description	Indication	Status
Phase I				
Bellicum Pharmaceuticals Inc., of Houston	BPX-601	Go-CAR T-cell candidate	Advanced, metastatic pancreatic cancer	Reported safety and activity in part 1 of phase I/II dose-escalation study in patients whose cancer expresses prostate stem cell antigen; 4 of 6 efficacy-evaluable patients treated with BPX-601 and a single dose of rimiducid had stable disease, with 2 patients demonstrating tumor shrinkage greater than 20%
Faron Pharmaceuticals Ltd., of Turku, Finland	Clevegen	Anti-Clever-1 antibody	Metastatic or inoperable solid tumors	First patient dosed in phase I/II MATINS study; first part of the trial deals with tolerability, safety and dose escalation to optimize dosing
Glenmark Pharmaceuticals Ltd., of Mumbai	GBR-1302	HER2xCD3 bispecific antibody	HER2-positive cancers	Data from first-in-human trial show pharmacokinetic profiles observed from doses of 30 ng/kg and beyond, with maximum concentration (Cmax) observed close to the end of infusion, after which serum concentrations declined bi-exponentially, with a mean terminal half-life of about 4 to 7 days; company plans study in HER2-positive breast cancer patients with weekly dosing regimen
Noxxon Pharma NV, of Berlin	NOX-A12 (olaptesed pegol)	Anti-CXCL12/ SDF-1 Spiegelmer	Metastatic, microsatellite stable pancreatic and colorectal cancer	Top-line data from the second part of ongoing study in combination with Keytruda (pembrolizumab, Merck & Co. Inc.) show 5 patients (25%) achieved stable disease according to RECIST criteria (22% PaC, 27% CRC)
Phase II				
Idera Pharmaceuticals Inc., of Exton, Pa.	Tilsotolimod	Toll-like receptor 9 agonist	Unresectable or metastatic melanoma	32.4% of patients evaluable for efficacy achieved partial response or better and 76.5% achieved disease control
Sensorion SA, of Montpellier, France	Seliforant (SENS-111)	Histamine type 4 receptor antagonist	Vertigo crises	Met its tolerability primary endpoint in a statistically significant manner; does not affect vigilance and cognitive performance during a motion stimulus
Phase III				
Pfizer Inc., of New York	PF-06482077	20-valent pneumococcal conjugate vaccine	Pneumonia vaccine	Program begun

Notes

For more information about individual companies and/or products, see Cortellis.

Regulatory actions for Dec. 14, 2018

Company	Product	Description	Indication	Status
Agile Therapeutics Inc., of Princeton, N.J.	Twirla (levonorgestrel/ ethinyl estradiol), also AG-200-15	Low-dose, once-weekly contraceptive patch	Contraception	Met with FDA's Division of Bone, Reproductive, and Urologic Products to discuss design of comparative wear study with Xulane (norelgestromin/ethinyl estradiol, Mylan NV)
Genmab A/S, of Copenhagen	Darzalex (daratumumab)	Monoclonal antibody	Multiple myeloma	Submitted sNDA to Japan's MHLW to treat newly diagnosed MM ineligible for autologous stem cell transplant, in combination with bortezomib (Velcade, Takeda Oncology Co.), melphalan and prednisone

Company	Product	Description	Indication	Status
Janssen Pharmaceutical Cos., unit of Johnson & Johnson, of New Brunswick, N.J.	Xarelto (rivaroxaban)	Factor Xa antagonist	Venous thromboembolism	Submitted sNDA to FDA to prevent VTE in acute medically ill patients
Pfizer Inc., of New York	Zirabev (bevacizumab)	Biosimilar to Avastin; anti-VEGF monoclonal antibody	Metastatic carcinoma of the colon or rectum; metastatic breast cancer; unresectable advanced, metastatic or recurrent non-small-cell lung cancer; advanced and/or metastatic renal cell cancer; persistent, recurrent or metastatic carcinoma of the cervix	EMA's Committee for Medicinal Products for Human Use recommended approval
Takeda Pharmaceutical Co. Ltd., of Osaka, Japan	Adcetris (brentuximab vedotin)	CD30-modulating ADC	Hodgkin lymphoma	EMA's CHMP issued positive opinion to extend marketing authorization, in combination with adriamycin/vinblastine/ dacarbazine, in previously untreated CD30+ stage IV Hodgkin lymphoma

Notes

For more information about individual companies and/or products, see Cortellis.

Bench Press

BioWorld looks at translational medicine

By Anette Breindl, Senior Science Editor

Gut bacteria eat, make neurotransmitter

In looking for ways to culture gut bacteria, researchers at Northeastern University have discovered that multiple species of gut bacteria are able to either produce or consume gamma-aminobutyric acid (GABA), the major inhibitory nervous system of the mammalian nervous system. Many species of gut bacteria cannot be cultured using standard mechanisms, and the authors hypothesized that this was because in the complex bacterial ecosystem of the gut, those species have learned to use metabolites produced by their neighbors. The team first showed that KLE1738, which requires the presence of *Bacteroides fragilis* to grow in culture, was dependent on *B. fragilis*-produced GABA, and then used genome-based metabolic modeling to identify "multiple genera with the predicted capability to produce or consume GABA." They also showed that the presence of *B. fragilis* was inversely correlated with host depression. The team concluded that their findings "suggest that microbial-derived GABA may influence the host, and are the first step in understanding the biology of this intriguing connection." They published their work in the Dec. 10, 2018, online issue of *Nature Microbiology*.

Irisin and bone: Good but complicated

A team from the Dana-Farber Cancer Institute has identified the receptor for the "exercise hormone" irisin in bone. Irisin is one of several hormones that muscles produce during exercise, and has been shown to mediate beneficial effects of exercise in several different tissues, including brain and fat. In their work, the team identified the alpha-5 integrin receptor as irisin's receptor in bones, and showed that irisin stimulated bone resorption by osteocytes. The authors wrote that in light of those findings, previous results showing that irisin might be beneficial in osteoporosis might be "counterintuitive," but suggested that irisin might function similarly to parathyroid hormone, with intermittent pulses having different effects than chronic high levels. They published their results in the Dec. 13, 2018, issue of *Cell*.

Premature birth complication prevented by targeting microglia

A team at Johns Hopkins Medical School has discovered that "Cognitive impairments induced by necrotizing enterocolitis can be prevented by inhibiting microglial activation in mouse brain," as they titled the paper reporting their results. Necrotizing enterocolitis (NEC) is a complication that occurs in about 10 percent of preterm infants, and babies that survive the NEC itself often develop severe neurological impairments. The team had previously shown that Toll-like receptor 4 (TLR4) activation in the gut contributed to NEC development. In their current work, they demonstrated that the endogenous ligands activating TLR4 in the gut also activated microglial cells in the brain, and that "an orally administered dendrimer-based nanotherapeutic approach to targeting activated microglia could prevent NEC-associated neurological dysfunction in neonatal mice. These findings shed light on the molecular pathways leading to the development of NEC-associated brain injury, provide a rationale for early removal of diseased intestine in NEC, and indicate the potential of targeted therapies that protect the developing brain in the treatment of NEC in early childhood," they wrote. Their work appeared in the Dec. 12, 2018, issue of *Science Translational Medicine*.

Less is more for durable STING effects

Activation of stimulator of interferon gamma (STING) is a bridge from innate immune responses, in the form of inflammation, to the activation of T cells, the major weapons of adaptive antitumor immunity. However, attempts to use STING agonists to stimulate robust antitumor immunity, which are in early clinical trials, have produced underwhelming results to date. Researchers from Aduro Biotech Inc. have conducted preclinical dosing studies and found that the doses that led to optimal adaptive immune responses and synergized best with checkpoint blockade were lower than those that led to the strongest innate immune responses. "Higher tumor ablative dosing regimens compromise durable antitumor immunity," the authors wrote. "A single relatively low dose of [intratumorally]-administered STING agonist produced the most tumor-specific T cells," while "intensive dosing regimens ablated injected tumors largely without the help of CD8+ T cells." Their work appeared in the Dec. 11, 2018, issue of *Cell Reports*.

Resolvin receptor analogues limit inflammation

Researchers from the NIH and Brigham and Women's Hospital have identified agonists of the receptor for resolvin D1 (DRV1), a protein that plays a key role in limiting inflammatory processes. Acute inflammation is a powerful protective mechanism, while chronic inflammation contributes to a myriad of diseases. The team had previously identified resolvin as important for preventing inflammation from turning chronic by actively shutting it off. However, resolvin itself is challenging to synthesize, making it unsuitable for therapeutic applications. The team screened nearly 50,000 small molecules and identified three chemotypes, and four individual compounds, that were able to strongly activate DRV1. The scientists wrote that the structures they have identified "offer molecular templates to facilitate clinical development of therapeutics that target human DRV1 and its role in the resolution of inflammation." Their work appeared in the Dec. 13, 2018, issue of *Cell Chemical Biology*.

Continues on next page

Bench Press

Continued from previous page

Zinc plus its transporter kill resistant bacteria

Scientists at the University of Queensland have shown that simultaneously treating bacteria with zinc, and the zinc ionophore PBT-2, killed bacteria at doses that were ineffective when either compound was used alone. Bacteria are dependent on zinc, but its levels need to be strictly controlled, with too much zinc being as much of a problem as too little. In their work, the team showed that several gram-positive infections could be treated through topical treatment with a combination of zinc and PBT-2 (hydroxyquinoline, Prana Biotechnology Ltd.). PBT-2 is in phase II trials and is being developed for both Alzheimer's disease and Huntington's disease, and the authors concluded that "the delivery of zinc using the ionophore PBT2 can reduce the concentration of zinc required for efficacy to levels that are tolerated physiologically (30). Taken together, these data demonstrate a new paradigm whereby destabilizing bacterial physiology may circumvent the antibiotic resistance problem, by rescuing the function of antibiotics to which bacteria have become resistant." The team published its findings in the Dec. 11, 2018, online issue of *mBio*.

LncRNAs are gene trainers

Scientists at the University of Cape Town have identified an important role for long noncoding RNAs (lncRNAs) in "training" innate immune system genes, leading to their rapid transcription in times of need. Chromatin associated with immune gene promoters often has an epigenetic mark, trimethylation at lysine 4 of histone 3, that enables their rapid transcriptional activation, a process known as trained immunity. The authors demonstrated that this trimethylation was enabled by a group on lncRNAs they had previously identified as immune-priming. LncRNAs can function by tethering distant parts of chromosomes together, and tethering them to proteins, to coordinate their activities. The team demonstrated that the immune-priming lncRNA UMLILO acted to direct the transcription factor MLL-1 to promoters that facilitated chemokine production, facilitating their epigenetic priming. The authors concluded that "adjustment of immune gene levels by directly altering the activity of [immune-priming lncRNAs] may represent a valuable therapeutic strategy to achieve tailored immunomodulation." Their work appeared in the Dec. 10, 2018, online issue of *Nature Genetics*.

Bacterial toxins weaken gut barrier

A team from Harvard Medical School and Sun Yat-Sen University has demonstrated that the two major *Clostridium difficile* toxins, imaginatively named toxin A and toxin B, led to elevated levels of vascular endothelial growth factor A (VEGF-A) during infection, which increased gut vascular permeability. The team showed that mice infected with toxin-producing *C. difficile* strains, but not with isogenic strains that did not produce toxin, had high levels of VEGF-A and increased vascular gut permeability, and that blocking VEGF-A or its downstream signaling could lessen the severity of *C. difficile* infection (CDI). "Our findings indicate critical roles for toxin-induced VEGF-A and colonic vascular permeability in CDI pathogenesis and may also point to the pathophysiological significance of the gut vascular barrier in response to virulence factors of enteric pathogens," the authors wrote. "As an alternative to pathogen-targeted therapy, this study may enable new host-directed therapeutic approaches for severe, refractory CDI." They published their findings in the Dec. 3, 2018, online issue of *Nature Microbiology*.

New tumor organoid includes microenvironment

Researchers at Stanford University have developed a method for culturing organoids consisting of tumor samples and their microenvironment, including B, T and natural killer cells. Organoids, culture systems that consist of multiple cell types, have allowed deep insights into cellular behavior in a system that combines the accessibility of cell culture with at least some of the complexity of an in vivo system. However, co-culturing tumors with their native infiltrating immune cells has so far remained an elusive goal. In their work, the team used an air-liquid interface that enabled them to develop a 3-dimensional culture of patient-derived tumors that preserved the patient immune cells gathered with the tumors. "Organoid-based propagation of primary tumor epithelium en bloc with endogenous immune stroma should enable immune-oncology investigations within the TME and facilitate personalized immunotherapy testing," the authors wrote. Their work appeared in the Dec. 13, 2018, issue of *Cell*.

HER mutations can cause ER resistance

The majority of breast cancers overexpress estrogen receptors (ER). Such tumors can be treated by targeting the ER, but resistance renders treatment successes temporary. Beyond mutations in the ER itself, resistance mechanisms of ER-overexpressing tumors remain poorly understood. Researchers from the Dana-Farber Cancer Institute have shown that one mechanism of resistance in patients with metastatic ER-positive breast cancer was the overexpression of HER2, and that adding the HER2 inhibitor Nerlynx (neratinib) to the treatment regimen could overcome resistance in such cases. Beyond pointing to possible therapeutic approaches to treating or preventing resistance, the authors noted that "the acquisition of targetable activating alterations in the metastatic setting highlights the importance of serial profiling of metastatic tumor biopsies or cell-free DNA from blood at the time of resistance." Their work appeared in the Dec. 10, 2018, issue of *Nature Genetics*.

Let us know what you think

We welcome your feedback. Contact Anette Breindl at anette.breindl@clarivate.com, or (770) 810-3134.