BioWorld

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

Clarivate Analytics

November 13, 2017
Volume 28, No. 220

IP talks underway with Merck, GSK

Savoring ACIP of victory, Dynavax looks ahead with Heplisav-B; price to come

By Randy Osborne, Staff Writer

After the approval last week of Dynavax Technologies Corp.'s Heplisav-B hepatitis B virus (HBV) vaccine, backers are looking forward to the launch in the first quarter of next year and the meeting of the Advisory Committee on Immunization Practices (ACIP), which can vote to add the vaccine to its "preferred" list for easier coverage by payers.

See Dynavax, page 3

House, Senate tax reform bills take aim at orphan drug credit

By Mark McCarty, Regulatory Editor

While there are important similarities, the U.S. Senate and the House of Representatives have taken different approaches to several matters in their respective tax reform proposals, including the tax credit for clinical studies of orphan drugs, which the Senate bill would cut substantially while the House bill would eliminate that tax credit altogether.

Makers of therapeutic and diagnostic devices may have hoped a repeal of the 2.3 percent medical device tax would find a place in the tax reform push, but Rep. Kevin Brady (R-Texas), chairman of the House Ways and Means Committee, has suggested a different approach. Brady said that any suspension or outright revocation of that tax, which is slated to go back into force in January 2018, will appear in the reauthorization of the Children's Health Insurance Program, the current authorization of which expires at the end of 2017.

See Tax reform, page 4

Israel's Entera Bio goes after U.S. listing in $50M IPO

By Marie Powers, News Editor

Entera Bio Ltd., established in June 2010 as a joint venture of fellow Israeli firms DNA Biomedical Solutions and Oramed Pharmaceuticals Inc., is seeking to raise up to $50 million, including overallotments, in an IPO, with a listing on Nasdaq under the ticker ENTX. The Jerusalem-based firm is developing oral formulations of teriparatide (parathyroid hormone, or PTH, 1-34) to treat hypoparathyroidism (EB-612) and osteoporosis (EB-613). Oppenheimer & Co. is the sole bookrunner on the deal, which was not priced.

At the company's launch, DNA Biomedical provided $600,000 in cash and Oramed licensed the use of certain patent rights related to oral delivery of drugs. Months later, Oramed sold most of its holdings in the startup to DNA Biomedical and converted the patent licenses to assignments in exchange for rights in the fields of diabetes and influenza and for royalties of 3 percent on net product revenues related to the intellectual property. DNA Biomedical and Oramed then terminated the joint venture and Entera set out on its own.

The company's drug candidate, teriparatide, isn't exactly a rare commodity. More than 25 versions

See Entera, page 5

Bench Press

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

Read this week's edition

The BioWorld Biome

Building neuronal roads

Axon assemblies pave way for drug discovery

By John Fox, Staff Writer

The creation of a new microdevice that allows generation of three-dimensional (3-D) axonal structures from human stem cell-derived neurons should facilitate future studies on axon development and allow drug screening for diseases including amyotrophic lateral sclerosis (ALS), a new study has found.

A collaboration between Japanese and American researchers at the University of Tokyo and Harvard

See Axons, page 6

Nanotech breakthrough?

Researchers leapfrog forward with 20x improvement in neuron-level brain monitoring

By Stacy Lawrence, Staff Writer

A nanotech-based brain implant with probes that are thinner than a human hair has been developed and tested by a coalition of scientists. Those researchers recently published in *Nature* about their work monitoring the brains of live rats and mice via the novel device, with silicon probes so tiny that insertion into a living brain causes very little damage.

Already, about 400 device prototypes are in the hands of researchers around the world with

See Nanotech, page 7

Financings

Erytech Pharma SA, of Lyon, France, priced its U.S. IPO of 4.7 million American depositary shares (ADSs) at $23.26 per ADS – its proposed range was $23 to $24 – and also raised $16 million in a European private placement. Jefferies, Cowen & Co. and Oddo BHF acted as lead managers on the deal. Shares of Erytech (NASDAQ:ERYP) closed Friday at $21.96. (See *BioWorld*, Oct. 10, 2017.)

Onconova Therapeutics Inc., sold 920,000 shares of its common stock for $1.50 per share, grossing the company approximately $1.38 million. The company plans to use the proceeds of the offering, which is expected to close on or about Nov. 14, to fund its clinical and preclinical programs, for other research and development activities and for general corporate purposes. Shares of Onconova (NASDAQ:ONTX) closed down 17.2 percent to $1.54 per share on Friday.

Sarepta Therapeutics Inc., of Cambridge, Mass., said the initial purchasers of its convertible senior unsecured notes that will mature on Nov. 15, 2024, have exercised their option to purchase an additional $95 million in notes, which is expected to close on Nov. 14, 2017. The notes have an interest rate of 1.5 percent and have an initial conversion price of approximately $73.42 per share. Sarepta also entered into privately negotiated capped call transactions with one or more of the options holders to reduce the potential dilution of the company's common stock upon conversion of the notes if the stock price is lower than the cap price which is initially $104.88 per share.

Other news to note

Aduro Biotech Inc., of Berkeley, Calif., said data from preclinical studies with ADU-1604, its humanized anti-CTLA-4 monoclonal antibody, were presented at the Society for Immunotherapy of Cancer meeting in National Harbor, Md. Data from those in vitro and in vivo studies demonstrate the potency of ADU-1604 and its ability to inhibit tumor growth and enhance T cell-dependent antibody responses. Researchers conducted in vitro and in vivo studies comparing ADU-1604 to benchmark anti-CTLA-4 antibodies 10D1 (ipilimumab) and CP-675,206 (tremelimumab). They demonstrated that ADU-1604 binds to a unique epitope on a human CTLA-4 (hCTLA-4) and is at least comparable to benchmarks in functionality. Data from in vivo studies using a well-established humanized mouse model of non-small-cell lung cancer and a nonhuman primate model, demonstrate that ADU-1604 inhibits tumor growth and enhances T-cell responses, respectively.

Aicuris Anti-Infective Cures GmbH, of Wuppertal, Germany, and **Merck & Co. Inc.**, of Kenilworth, N.J., said the EMA's Committee for Medicinal Products for Human Use recommended marketing approval in the European Union for Prevymis (letermovir), an antiviral medicine that prevents cytomegalovirus reactivation and disease in patients who receive immunosuppressant medicines following an allogeneic hematopoietic stem cell transplant. The drug gained FDA approval a day earlier. (See *BioWorld*, Oct. 10, 2017.)

Alpine Immune Sciences Inc., of Seattle, reported at the Society for Immunotherapy of Cancer's annual meeting in National Harbor, Md., immuno-oncology preclinical data characterizing the functional activity of molecules it successfully generated from its variant immunoglobulin domain (vIgD) platform. Several immuno-oncology molecules were functionally active via multiple mechanisms of action, including the demonstration of tumor suppression in an animal model. The poster described the vIgD domains in multiple therapeutic formats, including tumor-localized Fc fusion proteins, multicheckpoint inhibitors, and vIgDs fused with tumor-specific monoclonal antibodies.

BioWorld

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

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 Duncan (Senior Production Editor), 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, contact Chris Venezia toll free at (855) 260-5607 or, outside the U.S. and Canada, at (646) 522-6243, email christopher.venezia@clarivate.com.

For photocopy rights or reprints, please contact Chris Venezia toll free at (855) 260-5607 or, outside the U.S. and Canada, at (646) 522-6243, or by email at christopher.venezia@clarivate.com.

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

Business office

John Borgman (Director of Commercial Competitive Intelligence), Donald R. Johnston (Senior Director, Current Awareness),

Contact us

Jennifer Boggs, (770) 880-3631 | John Borgman, (831) 462 2510 | Anette Breindl, (770) 810-3134 | Michael Fitzhugh, (770) 810-3064 | Donald R. 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, (770) 361-4789

Dynavax

Continued from page 1

Berkeley, Calif.-based Dynavax's shares (NASDAQ:DVAX) closed Friday at $20.25, up 20 cents, the approval of Heplisav-B having been made public after the markets closed Thursday.

Cowen and Co. analyst Phil Nadeau said the Heplisav-B label "appears favorable, as it includes results from secondary efficacy endpoints vs. Engerix-B, data on patients with diabetes, and a relatively benign treatment of the adverse-event data. We continue to think that Dynavax is undervalued for Heplisav," he added in a research report.

During a conference call with investors, Dynavax CEO Eddie Gray talked about a recent meeting of ACIP that gave him cause to believe "the arrival of Heplisav-B and the data that we have in diabetics provides the opportunity for renewed impetus" with regard to such patients, considering the recommendation that health officials made a few years ago. "I think our expectation is that we will be the vaccine of choice for such patients, and we will pick that up as we get through the back end of 2018, [when] we're securing additional doses out of our manufacturing capacity," he said. "The low-hanging fruit resides in the traditional market, and we will tackle that initially."

Chief Medical Officer Robert Janssen said on the call that he "presented ACIP at the October meeting, but because they can only vote on approved vaccines, the vote was delayed until February."

Gray said that "everybody knows who the [other] vaccinees are, and those people who need to be vaccinated turn up. The marketing challenge for diabetics is a little different, in that it is more connected to ensuring diabetics understand their need to be vaccinated and they turn up for such vaccination. So it's a slightly different challenge."

Dynavax has "always said that we would keep an open mind as to the requirements of that different challenge," he added. "We do believe that the utilization of routes such as pharmacies offer real potential. Whether or not it requires some kind of traditional sales efforts to physicians who manage diabetic patients is, I think, as yet unclear. If it becomes clear that that's part of the mix, we'll address it in an appropriate way."

Empire Asset Management said in a report Friday that "although we expect a sales ramp in 2018, we believe that due to vaccine contracting, Heplisav-B's sales in 2019 and beyond will be more reflective of the need for this vaccine."

'Torturous' FDA review

The vaccine's approval was based on data from three phase III noninferiority trials in almost 10,000 adult participants who received the vaccine. Studies compared Heplisav-B administered in two doses over one month to HBV vaccine Engerix-B from Glaxosmithkline plc (GSK), of London, administered in three doses over a six-month schedule. In results from the largest experiment, which included 6,665 participants, Heplisav-B turned up a statistically significantly higher rate of protection of 95 percent compared with 81 percent for Engerix-B.

> *"Heplisav's torturous FDA review – which has spanned five years, two CRLs, and two VRBPAC meetings (not including a third that was cancelled) – has ended with the HBV vaccine's approval.*
>
> Phil Nadeau
> Analyst, Cowen and Co.

The news was good, too, in a subgroup analysis of 961 participants with type 2 diabetes, where Heplisav-B showed a statistically significantly higher rate of protection of 90 percent compared to 65 percent for the GSK product. Across the three trials, the most common local reaction was injection site pain (23 percent to 39 percent). The most common systemic reactions were fatigue (11 percent to 17 percent) and headache (8 percent to 17 percent).

In July, members of the FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC) debated an apparent cardiovascular (CV) signal that had garnered Dynavax its second complete response letter (CRL) for Heplisav-B. VRBPAC panelists voted 12-1 with three abstentions that the available data prove the vaccine safe enough for approval, although they said the CV factor should be explored more fully in a postmarketing study. (See *BioWorld*, July 31, 2017.)

Dynavax has not disclosed pricing for Heplisav-B, of which, Cowen's Nadeau noted, the firm "has a stock of 250,000 vaccines ready for packaging and distribution, and enough raw material to manufacture an additional 750,000 doses." The company will make more, starting in the second half of next year, and at launch will "disperse its sales force to cover more than 75 percent of targeted institutions," he wrote.

Asked during the conference call about an ongoing intellectual property dispute regarding Heplisav-B, Michael Ostrach, chief business officer, said he does not "expect the patents controlled by GSK and Merck will prevent us from marketing Heplisav-B, and although we don't discuss details of ongoing discussions, I think it's fair to say that all three companies would agree that the best outcome for all of us will be license agreements containing reasonable royalty terms or the equivalent. You'll recall that the GSK-controlled patents expire in June or about a quarter after our launch."

Kenilworth, N.J.-based Merck & Co. Inc.'s patent "expires about two and a half years after launch, [but] Merck's out of the market, based on their announcement, for all of next year," he said. Merck has said worldwide demand caused a shortage of its Recombivax-HB.

All in, Nadeau wrote, "Heplisav's torturous FDA review – which has spanned five years, two CRLs, and two VRBPAC meetings (not including a third that was cancelled) – has ended with the HBV vaccine's approval," which "marks an important milestone in Dynavax's history, and management should be congratulated for its persistence and determination." ♦

Tax reform

Continued from page 1

Section 3401 of the Tax Cuts and Jobs Act of 2017, which passed out of the Ways and Means Committee Nov. 9 via a 24-16 vote, includes an outright repeal of credit for clinical testing expenses for those drugs, and the bill stated that the provision would allow the U.S. Treasury to recoup $54 billion between 2018 and 2027.

The Senate orphan drug proposal would recoup nearly $30 billion over the 10-year projection, in part by reducing the tax credit to 25 percent if the sponsor incurred no clinical costs in any of the three years prior to a given tax year. As is the case with the House bill, the Senate provision would take force in tax years commencing after Dec. 31, 2017. Sen. Orrin Hatch, chairman of the Senate Finance Committee, said the committee would take up the bill on Nov. 13 in hopes of passing a bill out of committee by Nov. 17. "I'm confident that if we continue to allow each chamber the opportunity to work its will, we can easily reconcile" the differences between the House and Senate bills, Hatch said.

The House bill would drop the corporate tax rate to 20 percent, although companies bringing in less than $75,000 a year would be subject to a rate of only 9 percent. Personal service companies would pay a tax rate of 25 percent, suggesting a source of adversarial lobbying on the proposal in the weeks ahead, and the summary of the House bill states that this set of provisions would deprive the Treasury of $1.46 trillion over the 10-year projection.

The Senate bill likewise would apply a 20 percent tax rate to corporations, although there is no provision for companies with receipts of less than $75,000 a year. That would apply to tax years commencing after the end of 2018, a year after the related provisions of the House bill go into force.

Under the Modified Accelerated Cost Recovery System (MACRS), the depreciation schedule in the House bill allows full depreciation of qualified expenses in the first year, although that would be applied retroactively to Sept. 27, 2017, and would expire at the end of 2022. That would take $25 billion out of the Treasury. The Senate bill's depreciation feature invokes a more complex mechanism, allowing a depreciation of 50 percent in the first year (2017), followed by depreciation rates of 40 percent and 30 percent in the two following years.

The amount of one-year, small business expensing under Section 179 of the Internal Revenue Code would grow from $500,000 to $5 million under the House bill, although that amount would continue to be indexed to inflation. That provision would remove $11.4 billion from the Treasury over 10 years. The Senate version is far less generous, allowing an immediate expensing of $1 million and a phase-out of $2.5 million rather than the phase-out amount of $25 million seen in the House bill.

The House bill uses a dividend-exemption system to deal with repatriation of income from foreign subsidiaries of U.S. corporations, exempting from taxation all of the foreign-source portion of dividends paid by a foreign corporation to a U.S. corporate shareholder, so long as that U.S. shareholder owns 10 percent or more of the foreign corporation. That provision would be in force for any distributions made after the current calendar year. Broadly speaking, the Senate bill provides a similar approach to encourage repatriation of overseas earnings to the U.S.

Jim Greenwood, president and CEO of the Biotechnology Innovation Organization (BIO), said the House bill's inclusion of several features, including a territorial tax system, would "make the U.S. more competitive on the world stage and support domestic manufacturing and job creation." Nonetheless, Greenwood said the association will urge Congress to maintain the orphan drug tax credit as well as "the inclusion of incentives for pre-revenue innovation and for the development of advanced biofuels, renewable chemicals and biobased products."

BIO's senior vice president for communication, Ken Lisaius, said the Senate proposal would "make the U.S. more competitive on the world stage and support American jobs and manufacturing." Lisaius stated also that BIO members are "pleased that the [Finance] Committee recognized the important role" of the orphan drug tax credit, noting that BIO will continue to work with Congress "to ensure that this vital incentive remains as effective as under current law." ♦

Other news to note

Amgen Inc., of Thousand Oaks, Calif., and **Allergan plc**, of Dublin, said the EMA's Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion for the marketing authorization of ABP-215, a biosimilar to Avastin (bevacizumab, Roche Holding AG). The product has been recommended for approval for the treatment of several types of cancer, including in combination with fluoropyrimidine-based chemotherapy for metastatic carcinoma of the colon or rectum; and in combination with paclitaxel for metastatic breast cancer. In separate news, Amgen said the CHMP adopted a positive opinion to expand the current indication for Nplate (romiplostim) to include the treatment of chronic immune (idiopathic) thrombocytopenic purpura for patients 1 year of age and older who are refractory to other treatments (e.g., corticosteroids, immunoglobulins).

Astrazeneca plc, of Cambridge, U.K., and its biologics research and development arm, Medimmune, said the EMA's Committee for Medicinal Products for Human Use adopted a positive opinion, recommending the marketing authorization of benralizumab as an add-on maintenance treatment in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus long-acting beta-agonists. If approved, the product will be available as a once-every-eight-week fixed-dose subcutaneous injection via a prefilled syringe.

Appointments and advancements

Biophytis SA, of Romainville, France, appointed Thomas Voit to its scientific advisory board.

Intec Pharma Ltd., of Jerusalem, named Walt Linscott chief administrative officer.

Entera

Continued from page 1

of the PTH receptor agonist are in development or on the market, according to Cortellis Competitive Intelligence. They range from Eli Lilly and Co. Inc.'s osteoporosis drug, Forteo, which commanded $1.5 billion in 2016 sales, to some dozen biosimilars and to candidates formulated as nasal sprays or nano-enabled delivery systems.

Nevertheless, Entera snagged orphan drug designation from the FDA and EMA for its oral teriparatide to treat hypoparathyroidism. A pivotal trial of the drug is expected to begin enrolling patients in the first half of next year, yielding top-line data in the first half of 2020. Entera plans regulatory submissions the same year.

Among the few approved options to treat hypoparathyroidism, Shire plc's Natpara, a once-daily injectable form of PTH, is the market leader, with $85.3 million in 2016 sales. The product was developed by NPS Pharmaceuticals Inc., which Dublin-based Shire snagged just weeks before Natpara's 2015 approval. (See *BioWorld Today*, Jan. 13, 2015, and Jan. 27, 2015.)

Entera maintains that EB-612, with its oral delivery, offers customized administration and flexible dosing regimens that improve efficacy and reduce the risk of serious side effects compared to the once-daily injectable. The company cited studies performed by NIH researchers showing that the total daily PTH dose required to maintain serum calcium in the normal or near-normal range was reduced by 50 percent with twice-daily PTH (1-34).

Those studies also showed that twice-daily dosing achieved better control over serum calcium and urinary calcium excretion compared to once-daily dosing.

Entera reported that the phase IIa trial of EB-612, completed in 2015, met its primary endpoints. Seventeen participants completed the four-month study, and no confirmed related serious or significant adverse events were reported. Entera also said that EB-612 showed the potential for similar efficacy to Natpara, based on findings from the pivotal REPLACE study used by NPS to seek approval. Entera plans to confirm the correlation in its phase IIb/III trial, which will use the same endpoints as REPLACE to assess the dosage, effectiveness and safety profile of EB-612 in an expanded patient population at multiple trial sites.

In short, EB-612 could offer the potential to become the standard of care for hypoparathyroidism, according to the company.

A phase I study of osteoporosis candidate EB-613 also is complete, with initiation of a phase IIa study expected in the first quarter of 2018. Following proof of concept, Entera will seek to attract a strategic partner to complete development and commercialization.

The company is studying the same agent to treat non-union fractures and plans to initiate a phase IIa study next year in that indication.

Proceeds from the IPO will fund R&D programs for both lead candidates, for which Entera holds global rights in the indications.

The company also plans to apply its technology platform to the oral delivery of other protein and large molecule therapeutics, initially with a focus on products based on previously approved agents. In its SEC filing, the company said it has conducted initial feasibility studies with multiple candidates and expects to begin development of a non-PTH candidate by the end of next year.

Founding CEO Phillip Schwartz has a background in big and specialty pharma, with previous roles at EMD Serono and Endo International plc. Miriam Blum, chief medical officer since Entera's inception, came from academia, serving as associate professor and attending physician at Tufts University Medical School and the New England Medical Center. Hillel Galitzer, the company's chief operating officer, and Mira Rosenzweig, chief financial officer, round out the management team.

Luke Beshar, executive chairman of Entera's board, previously served as chief financial officer and executive vice president of NPS.

Since its inception, Entera has raised $18.3 million, according to its filing, including $12.4 million last month from sales of series B preferred shares.

DNA Biomedical remains the largest shareholder. In its F-1, Entera reported $12.8 million in cash and equivalents as of Nov. 1 and an accumulated deficit of $34.4 million as of June 30. ♦

Other news to note

Bristol-Myers Squibb Co., of New York, said the FDA has expanded the indication for Sprycel (dasatinib) tablets to include the treatment of children with Philadelphia chromosome-positive chronic myeloid leukemia (CML) in chronic phase (CP). The approval was granted under priority review, and the indication received orphan drug designation from the FDA. The safety and efficacy of Sprycel in pediatric patients were found favorable in two pediatric studies of 97 patients with CP-CML: an open-label, non-randomized, dose-ranging trial and an open-label, non-randomized, single-arm trial. Among the 97 patients in the two studies, 51 patients (exclusively from the single-arm trial) had newly diagnosed CP-CML, and 46 patients (17 from the dose-ranging trial and 29 from the single-arm trial) were resistant or intolerant to previous treatment with Gleevec (imatinib, Novartis AG).

ERS Genomics Ltd., of Dublin, and **Cellecta Inc.**, of Mountain View, Calif., said they entered a nonexclusive license agreement that provides Cellecta with worldwide access to ERS Genomics' CRISPR/Cas9 genome editing intellectual property for use in informing research tools and services. Cellecta is the first commercial provider of a lentiviral-based CRISPR library targeting all 19,000+ human protein-coding genes, and utilizes RNAi and CRISPR technologies for the discovery and characterization of therapeutic targets. Financial details of the agreement were not disclosed.

Axons

Continued from page 1

University led to the development of the new microdevice, with the study being reported in the Oct. 26, 2017, edition of *Stem Cell Reports*.

Axons are the cellular structures through which neurons transmit information to other cells. In the body, axons assemble to form small bundles known as fascicles.

"Axons form fascicles in many different areas of the body, including in the motor and sensory nerves, and in the central nervous system," study leader Yoshiho Ikeuchi, a lecturer at the Institute of Industrial Science at the University of Tokyo, told *BioWorld*.

"Axons or axonal fascicles transmit action potentials to operate our bodies," he said. "In the present study, we focused on motor nerves, which transmit electrical signals from the spinal cord to the skeletal muscle."

Several technologies allow scientists to generate and study single axons in the laboratory, but no techniques have so far succeeded in creating nerve fascicles.

The newly developed microdevice is expected to provide important insights into brain development and disease management.

"We know that growing axons form fascicles, but we do not know how fascicles form," said Ikeuchi, noting that while many scientists have examined axon development and degeneration in two-dimensional systems, it is increasingly clear that the fascicle's 3-D structure plays an essential role in axonal function.

Because fascicles are disrupted in many neurodegenerative diseases such as ALS, the researchers theorized that understanding their formation could give clues on the prevention of ALS and other diseases.

"Besides ALS, this new technology should prove useful in the treatment of other motor neuron diseases and perhaps even aging itself," said Ikeuchi. "Hopefully, in the future we would like to explore the possibility of using the axon fascicles in regenerative medicine."

The researchers created a microdevice, into which a spheroid comprising human neurons derived from induced pluripotent stem (iPS) cells was placed. A microchannel narrow enough to align axons and allow them to bind to each other, led to formation of fascicles showing properties consistent with those seen in human brains.

Spheroids were placed in the microdevice's chamber, from which axons grew, with some axons spontaneously entering the microchannels. The nature of the molecular signaling causing the entry of axons into the microchannels remains unknown, but fascicles were detected in more than 90 percent of experiments, establishing the value of the microdevice design.

"This is the first stem cell-based technique to have successfully created nerve fascicles in a controlled manner," noted Ikeuchi. "By creating a structure and microenvironment similar to that of neurons cultured outside the body, we should have a better way of analyzing physiological changes and responses of axon fascicles to external stimuli.

"The device gives us a means to investigate which factors are responsible for fascicle assembly," he added.

The researchers then simulated neurodegenerative conditions by introducing peroxide into the microchannels, to which the fascicles responded with morphological changes.

"Use of peroxide to simulate neurodegenerative conditions is a standard method used to damage neurons in a way that mimics the physiological damages in our bodies, albeit on an accelerated time scale," explained Ikeuchi.

"Specifically, we observed that the surface of the axon fascicles became significantly rougher after peroxide treatment, in which presumably the axons were broken," he said.

"It is very easy to quantify surface roughness with pre-existing image analysis software, which makes the technique particularly suitable for drug screening," he noted.

Those new findings, together with the relative ease of the experiments, suggest that the new microdevice will be applicable for testing experimental drug compounds that might prevent fascicle degeneration caused by disease.

'Such motor nerve organoids can be used for drug screening," said Ikeuchi. "We intend to use this new technology to promote drug discovery, make motor nerve organoids mimic actual nerve functions more closely, and use it to mimic the body's other axonal fascicles." ♦

Other news to note

Halozyme Therapeutics Inc., of San Diego, said presented nonclinical data at the Society for Immunotherapy of Cancer annual meeting in National Harbor, Md., which demonstrate the potential for PEGPH20, its pegylated recombinant human hyaluronidase, to increase the infiltration of immune cells into the tumor microenvironment and enhance the efficacy of immuno-oncology drugs in an HA-accumulating murine colon tumor model. The study showed that degradation of hyaluronan (HA) in a tumor by PEGPH20 can facilitate an antitumor immune response induced by checkpoint blockade by promoting effector cell infiltration and skewing the immune microenvironment toward a more antitumor composition. The data support Halozyme's ongoing clinical evaluation of PEGPH20 in combination with checkpoint inhibitors.

Appointments and advancements

Magenta Therapeutics Inc., of Cambridge, Mass., appointed Charlotte McDonagh vice president, biotherapeutics; Cindy Driscoll vice president, finance; Karen Nichols vice president, regulatory and quality; Manisha Pai vice president, investor relations and communications; and Zoran Zdraveski senior vice president, chief legal officer and corporate secretary.

Proqr Therapeutics NV, of Leiden, the Netherlands, appointed Peter Adamson senior vice president ophthalmology franchise, and Robert Friesen senior vice president science and early development. Chief Development Strategy Officer David M. Rodman will assume leadership over clinical development.

Nanotech

Continued from page 1

another 100 slated to be deployed before the end of the year. Known as Neuropixels, the probes are expected to revolutionize understanding of the brain. Any potential human research is likely to start in patients with severe brain disorders, such as epilepsy, who already require invasive surgery.

"People were just wildly enthusiastic, in fact the demand has been tremendous. They are 20 times better than the alternative. And that's enough better that everybody who can get their hands on them abandons the alternative and does this instead," Timothy Harris, who has led the Neuropixels collaboration, told *BioWorld*. He is the director of the Applied Physics and Instrumentation Group at the Ashburn, Va.-based Janelia Research Campus for the Howard Hughes Medical Institute (HHMI).

Researchers worked with Belgian nanotechnology fabricator Imec to get the probes built. The development and testing of Neuropixels was funded with $5.5 million from HHMI, as well as the Washington-based Allen Institute for Brain Science, the Gatsby Charitable Foundation, University College London (UCL) and the Wellcome Trust.

> *"People were just wildly enthusiastic, in fact the demand has been tremendous. They are 20 times better than the alternative.*
>
> Timothy Harris, Director, Applied Physics and Instrumentation Group, Janelia Research Campus for the Howard Hughes Medical Institute

The Neuropixels probes are being used in unprecedented ways, including in a multicounty effort from a coalition known as The International Brain Lab. Groups of researchers from the U.K, U.S., France, Switzerland and Portugal are participating to collaboratively monitor all the regions of the living mouse brain.

Each lab is focused on a specific area of the brain and all the data are being pooled in real-time across the labs to represent fully the living mouse brain. Altogether they are simultaneously recording activity from 1,000 neurons in mice as they each perform the same task, foraging for food.

By pooling data from multiple labs, they can make measurements in all areas of the brain at a cellular level: simultaneously recording activity from 1,000 neurons in mice performing exactly the same task. The labs are then sharing their data in real time, enabling them to look at exactly what's happening in neurons distributed throughout an entire brain.

"To understand the brain we need to understand how a lot of neurons spread all over the brain work together. Until recently, it was possible to measure the activity of individual neurons within a specific spot in the brain or to reveal larger, regional patterns of activity, but not to do both at the same time," said Matteo Carandini, a Wellcome investigator and neuroscientist at UCL. "These probes are a game-changer. If you place them appropriately, you can really study how different parts of the brain work together at the neuronal level."

Design details

The top two design priorities for the Neuropixels probes were that they offer "dense and extensive recording sites to isolate individual neurons across large regions of the brain" and "a small cross-sectional area to minimize brain tissue damage," according to the *Nature* paper. Other priorities included low noise, resistance to movement artifacts or other interference, efficient data transmission, long-term recording stability and low-cost, scalable fabrication.

The rodent probes are 10 millimeters long, about the same size as a mouse or rate brain; they are 70x20 micrometers wide with 100 recording sites per millimeter. Researchers used two probes to simultaneously record more than 700 single neurons from five mouse brain structures. The rodent studies reported in *Nature* each successfully used the implanted probes for at least eight weeks.

The fully integrated functionality and small size of Neuropixels probes allowed large populations of neurons from several brain structures to be recorded in freely moving animals.

"This combination of high-performance electrode technology and scalable chip fabrication methods opens a path towards recording of brain-wide neural activity during behavior," concluded the paper.

The Neuropixels technology obviously generates massive quantities of data, making analytics a top priority to be able to grasp all of the information gleaned. The probe automatically transforms the detected electrical signals into digital data that are ready for computational analysis. After being initially drowned in a flood of data, UCL researchers developed data analytics, which have also been made available to other scientists, capable of translating all those data into meaningful information on brain cell activity.

Listening to thunder

Harris offered an analogy to better understand the data being observed on the activity of a single neuron. "Your brain cells are electrical devices; they send signals via electricity. What happens when a neuron activates, it is sending signals to a bunch of other neurons and it does this by changing the charge within itself.

"What happens is that a very faint but detectable electrical signal is emitted in the local vicinity as sort of an unintended consequence. That's not the information itself; that goes along the way to the next neuron. But the way that it generates the signal, it's a bit like lightning and thunder; the cells are making lightning and we are listening to the thunder," he added.

Up next, on the redesign front, is a probe with four shanks and a smaller base in order to make it more wieldy for long-term use and recordings. The team also is working on designing a larger version for use in primates.

Harris expects that a decade from now Neuropixels probes will be widely used in nonhuman primate experimentation, as

See Nanotech, page 8

Nanotech

Continued from page 7

well as an experimental device in humans. He said he's already being approached by neurosurgeons who are conducting invasive brain surgeries and are interested in incorporating the technology, for example, in epilepsy patients whose conditions are so severe as to require the removal of a portion of the brain.

"What has surprised me is the magnitude of change in people's thinking," summed up Harris. "This has been such a large change that whole new research projects have been planned because it's available.

"As far as I can tell, the availability of these devices is going to make what people do different. The popularity of these things is a little bit alarming. They have gone from being successful to too hyperbolic and fashionable," he concluded. "I've been there before with technology advancements. So, I'm waiting for the hubbub to die down and for the scientists to get back to work on what's genuinely realistic. But it's a big change in the way people think about using these kinds of tools." ♦

Other news to note

Heron Therapeutics Inc., of San Diego, said the FDA has approved Cinvanti (aprepitant) injectable emulsion, for intravenous infusion. The drug is a substance P/neurokinin-1 (NK1) receptor antagonist, indicated in adults, in combination with other antiemetic agents, for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC), including high-dose cisplatin, and nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC). Aprepitant (including its prodrug, fosaprepitant) is the only single-agent NK1 receptor antagonist to significantly reduce chemotherapy-induced nausea and vomiting (CINV) in both the acute phase (0-24 hours after chemotherapy) and the delayed phase (24-120 hours after chemotherapy). Cinvanti was approved based on data demonstrating its bioequivalence to Emend IV (fosaprepitant), supporting its efficacy for the prevention of acute and delayed CINV following HEC and MEC.

Inotrem SA, of Paris, entered an R&D collaboration agreement with the diagnostics unit of Basel, Switzerland-based **Roche Holding AG** to develop a companion diagnostic test using a soluble plasma circulating protein (sTREM-1) developed by Inotrem and the Roche Elecsys platform. It is Roche Diagnostics' first collaboration agreement with a startup biotech company. The firms will work together to develop an in vitro robust prototype assay for quantitative measurement of sTREM-1 in plasma samples of septic shock patients. STREM-1 is a marker of the activation of the TREM-1 immune amplification pathway and high sTREM-1 plasma concentrations have been shown to be associated to a negative outcome in septic shock patients, the company said. Terms were not disclosed.

Sangamo Therapeutics Inc., of Richmond, Calif., disclosed plans for new corporate headquarters in an 88,000-square-foot building at Oyster Point in Brisbane, Calif., with occupancy of the site expected in late 2018, after completion of architectural improvements. The company will retain its Point Richmond location as a Sangamo Research Center.

Sunovion Pharmaceuticals Inc., of Marlborough, Mass., said the FDA accepted for review its NDA for dasotraline, a dual-acting dopamine and norepinephrine reuptake inhibitor being evaluated for the treatment of attention deficit hyperactivity disorder (ADHD) in children, adolescents and adults. The submission is supported by multiple placebo-controlled safety and efficacy studies, as well as two long-term studies that assessed the safety of dasotraline in people with ADHD for up to one year. (See *BioWorld Today*, Oct. 2, 2016.)

Therapix Biosciences Ltd., of Tel Aviv, Israel, executed a nonexclusive material transfer agreement with Yissum, the technology transfer company of the Hebrew University of Jerusalem, for two synthetic cannabinoids. Therapix plans to initiate a preclinical study during the fourth quarter to evaluate the opioid-sparing effect of those compounds in a rat model, the company said. Based on research surrounding the effects of the endocannabinoid system and how cannabinoids can play a role in pain relief, scientists have synthesized cannabinoids with improved binding affinity and target specificity, which do not cause the therapeutically undesirable cannabis psychoactivity, the company said. Terms were not disclosed.

Valeant Pharmaceuticals International Inc., of Laval, Quebec, completed the sale of the Obagi Medical Products business for $190 million in cash to Haitong International Zhonghua Finance Acquisition Fund I LP and its affiliate **Obagi Cosmeceuticals LLC**, of Irvine, Calif. Valeant will use approximately $180 million of the net proceeds from the sale to repay term loan debt under its senior credit facility. With the closing of the Obagi deal, the firm has reduced its total debt by more than $6 billion since the end of the first quarter of 2016, Valeant said.

VBI Vaccines Inc., of Cambridge, Mass., presented new preclinical data demonstrating the potency of VBI-1901 as a therapeutic vaccine candidate against glioblastoma multiforme (GBM) at the annual meeting of the Society for Immunotherapy of Cancer in National Harbor, Md. The data confirm that the use of intradermal delivery of VBI's enveloped virus-like particle, VBI-1901, may be a potent "off-the-shelf" dendritic cell vaccine. Following intradermal injection of VBI-1901, migratory dendritic cells at the injection site were confirmed to stimulate potent, adaptive T-cell immunity, the company said. The FDA recently accepted VBI's IND for VBI-1901, and the company expects to initiate enrollment in a multicenter phase I/IIa study evaluating VBI-1901 in patients with recurrent GBM in the fourth quarter of 2017.

Vertex Pharmaceuticals Inc., of Boston, said the EMA's Committee for Medicinal Products for Human Use issued a positive opinion recommending approving Orkambi (lumacaftor/ivacaftor) as a treatment for children with cystic fibrosis ages 6 through 11 who have two copies of the F508del mutation. An expanded approval, which still needs to be ratified by the European Commission, would make approximately 3,400 additional patients eligible for the medicine in Europe.

Other news to note

Zydus Cadila, of Ahmedabad, India, said the Mexico regulatory authority, COFEPRIS, granted marketing approval to Lipaglyn (saroglitazar magnesium) as a treatment for dyslipidemia in patients with type 2 diabetes and for hypertriglyceridemia in type 2 diabetics not controlled by statins. Lipaglyn is a PPAR-alpha/gamma agonist that has been on the market in India since September 2013.

Appointments and advancements

Selecta Biosciences Inc., of Watertown Mass., appointed John Leaman chief financial officer and head of corporate strategy, and Stephen Smolinski chief commercial officer.

Topas Therapeutics GmbH, of Hamburg, Germany, named Rupert Sandbrink chief development officer and chief medical officer.

In the clinic

Alexo Therapeutics Ltd., of Dublin, reported data from a phase I trial testing ALX-148 in patients with advanced malignancy at the Society for Immunotherapy of Cancer meeting in National Harbor, Md. As of October 2017, ALX-148 had been given to 17 patients at doses from 0.3 mg/kg to 30 mg/kg with one treatment-related serious adverse event, a patient with neutropenia plus infection at the 3-mg/kg dose. Once the single-agent portion of the trial concludes, Alexo plans to combine ALX-148, an engineered high affinity CD47 binding domain of SIRP-alpha linked to an inactive Fc region of human immunoglobulin, with checkpoint inhibitors and targeted cancer antibodies.

Alnylam Pharmaceuticals Inc., of Cambridge, Mass., said it reached alignment with the FDA during a type A meeting on safety measures and a risk mitigation strategy to enable resumption of dosing in clinical studies with fitusiran, including the phase II open-label extension study and the ATLAS phase III program. The FDA will now consider removal of the clinical hold upon final review of the amended protocols and other trial materials. Fitusiran is an investigational RNAi therapeutic targeting antithrombin for the treatment of patients with hemophilia A and B. Alnylam suspended patient dosing in the fitusiran trials in September following reports of a fatal thrombotic event. (See *BioWorld*, Sept. 8, 2017.)

Arena Pharmaceuticals Inc., of San Diego, said it completed full enrollment in the phase II study of etrasimod (APD-334), an oral, next-generation sphingosine-1-phosphate receptor modulator in development for autoimmune diseases. The trial, which enrolled 157 patients with moderate to severe ulcerative colitis, is a 12-week, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging trial evaluating safety and tolerability. Efficacy endpoints include improvement in the Mayo clinical score, response, remission and mucosal healing vs. placebo, and dose response.

Blueprint Medicines Corp., of Cambridge, Mass., reported data from a phase I trial testing BLU-285, a KIT and PDGFR-alpha inhibitor, in patients with advanced gastrointestinal stromal tumors at the Connective Tissue Oncology Society 2017 Annual Meeting in Maui, Hawaii. BLU-285 produced radiographic tumor reductions in 67 percent of patients treated with doses of 300 mg to 400 mg. That dose produced an objective response rate (ORR) of 17 percent and median progression-free survival (PFS) of 11.5 months. In patients with PDGFR-alpha D842 mutations, BLU-285 produced an ORR of 71 percent and an estimated 12-month PFS of 78 percent. In patients with KIT mutations, radiographic tumor reductions were observed in 67 percent of patients, the ORR was 17 percent by mRECIST 1.1 criteria, and the median PFS was 11.5 months. Blueprint plans to start a phase III trial in patients with PDGFR-alpha D842V mutations in the first half of 2018.

Boehringer Ingelheim GmbH, of Ingelheim, Germany, reported results from a descriptive phase IIIb lung imaging study at the Pulmonary Fibrosis Foundation Summit in Nashville, Tenn., providing evidence for the first time that Ofev (nintedanib) slowed the fibrotic process vs. placebo in people with idiopathic pulmonary fibrosis (IPF). The study showed a reduction in the development of lung fibrosis among people treated with Ofev, as measured by quantitative lung fibrosis score (QLF), which uses high resolution CT imaging to measure the extent of lung fibrosis. Lower QLF scores indicate less fibrotic progression in the lung. QLF score from baseline to six months was 11.4 percent in people treated with Ofev vs. 14.6 percent in the placebo group – the exploratory endpoint was not statistically significant. Ofev gained approval for IPF in 2014. (See *BioWorld Today*, Oct. 17, 2014.)

Bristol-Myers Squibb Co., of New York, reported updated results at the Society for Immunotherapy of Cancer meeting in National Harbor, Md., for PD-1 inhibitor Opdivo (nivolumab) plus BMS-986205, a selective, once-daily oral indoleamine 2,3-dioxygenase 1 inhibitor, from the ongoing phase I/IIa dose-escalation and expansion study, CA017-003. In the dose-escalation phase, the maximum tolerated dose of BMS-986205 in combination with Opdivo was 200 mg, and the recommended dose for further study was determined to be 100 mg. In the dose-expansion phase, findings for antitumor activity were reported in two cohorts – heavily pre-treated bladder (n=25) and cervical cancer patients (n=22). In the bladder cancer cohort, the objective response rate (ORR) and disease control rate (DCR) were 32 percent and 44 percent, respectively. In the cervical cancer cohort, the ORR was 14 percent and DCR was 64 percent.

Deciphera Pharmaceuticals Inc., of Waltham, Mass., presented data at the Connective Tissue Oncology Society meeting in Maui, Hawaii, from its ongoing phase I trial of DCC-2618, its pan-KIT and PDGFRalpha inhibitor, showing that in heavily pretreated patients with gastrointestinal stromal tumors, treatment with DCC-2618 at >100 mg daily resulted in disease control rates of 76 percent at 12 weeks and 57 percent at 24 weeks.

In the clinic

Eli Lilly and Co., of Indianapolis, said data published in *The Lancet* show that treatment with Forteo (teriparatide) for 24 months was associated with significantly fewer vertebral and clinical fractures (a composite of painful vertebral and nonvertebral fractures) compared with risedronate, a widely used oral bisphosphonate, in postmenopausal women with severe osteoporosis (5.4 percent vs. 12 percent; $p < 0.0001$) in the phase IV VERO trial.

Infinity Pharmaceuticals Inc., of Cambridge, Mass., reported data at the Society for Immunotherapy of Cancer meeting in National Harbor, Md., from the recently completed monotherapy dose-escalation component of the phase 1/1b study, which demonstrated that IPI-549 dosed once daily was well-tolerated and clinically active. Among 18 patients evaluable for activity, there was a 44 percent clinical benefit rate, defined as patients who had remained on treatment for at least 16 weeks, including one partial response in a patient with advanced peritoneal mesothelioma. Additionally, initial translational data from patient blood samples demonstrated that IPI-549 treatment results in immune stimulation, with early evidence of biological activity correlating with clinical benefit. IPI-549 is a PI3K-gamma inhibitor.

Intelgenx Corp., of Saint-Laurent, Quebec, submitted a clinical trial application to Health Canada for approval to initiate its phase IIa proof-of-concept study with montelukast in mild to moderate Alzheimer's disease (AD). The study with the leukotriene receptor antagonist is to be conducted at eight study sites, and will measure several safety and efficacy endpoints following daily dosing for 26 weeks. Intelgenx is working to repurpose montelukast as a therapeutic to treat neurodegenerative diseases such as AD by reformulating the drug into an oral film-based product. Currently, montelukast is marketed as Singulair, a once-daily tablet for the chronic treatment of asthma and seasonal allergic rhinitis.

Irx Therapeutics Inc., of New York, presented preliminary results at the Society for Immunotherapy of Cancer's meeting in National Harbor, Md., from a phase Ib trial of IRX-2, its lead candidate, in early stage breast cancer, which demonstrated the drug, a primary cell-derived biologic, is well-tolerated and showed early signs of activity. Results indicate that IRX-2 modulates the tumor microenvironment in early stage breast cancer cells and increases stromal tumor-infiltrating lymphocytes, T-cell activation, T-regulatory cell depletion and up-regulates PD-L1. Final results from the trial are expected next year.

Medicinova Inc., of La Jolla, Calif., said it plans to initiate a biomarker study for evaluating MN-166 (ibudilast) in methamphetamine (MA) use disorder. The proposed trial will evaluate MN-166 as a potential treatment for individuals diagnosed with MA use disorder with or without post-traumatic stress disorder. The study has already completed FDA review and will be initiated at Portland VA Medical Center and Oregon Health & Science University. MN-166 is a first-in-class, orally bioavailable, small-molecule phosphodiesterase-4 and -10 inhibitor and a macrophage migration inhibitory factor inhibitor that suppresses pro-inflammatory cytokines and promotes neurotrophic factors, the company said.

Pfenex Inc., of San Diego, reported in its third-quarter earnings interim pharmacokinetic (PK) results from ongoing Study PF708-301, which compares the effects of PF-708 and Forteo (teriparatide, Eli Lilly and Co.) in osteoporosis patients. PF-708 is a teriparatide candidate being developed through the 505(b)(2) regulatory pathway in the U.S. Data show the PF-708 and Forteo PK profiles are comparable, and there are no statistically significant differences in key PK parameters. Top-line immunogenicity data are expected in the first half of 2018.

Vascular Therapies Inc., of Cresskill, N.J., reported data from the phase III trial testing its sirolimus-eluting collagen implant on patients undergoing an arteriovenous fistula. Results from the first 18 open-label patients were consistent with the phase II trial where the median time until the fistula was ready for dialysis was 42 days and 76 percent of the fistulae were suitable for dialysis at six months. Vascular Therapies is enrolling patients in the randomized controlled portion of the phase III trial, with top-line results expected in 2019.

X4 Pharmaceuticals Inc., of Cambridge, Mass., presented data at the Society for Immunotherapy of Cancer meeting in National Harbor, Md., primarily generated from biopsies of tumors from melanoma patients, demonstrating changes in the tumor microenvironment and the activation of tumor-specific immune cell responses following oral administration of X4P-001-IO, a CXCR4 antagonist. Results showed early evidence of enhanced immune cell infiltration and activation in the tumor microenvironment as a single agent, including increases in cytotoxic CD8-positive T cells, increases in granzyme B, a marker of immune-mediated cell killing, and an increased interferon-gamma signature and PD-L1 levels supporting the use of X4P-001-IO in combination with anti-PD-1 checkpoint inhibitor therapy. A separate presentation of preclinical findings demonstrated single-agent antitumor activity from CXCR4 inhibition in the syngeneic B16-OVA melanoma model, with enhanced efficacy when added to checkpoint inhibitor therapy.

Bench Press

BioWorld looks at translational medicine

By Anette Breindl, Senior Science Editor

Time heals all wounds, especially daytime

Fibroblasts are the major cell type that is responsible for wound healing, as they migrate to the sites of injuries and secrete extracellular matrix molecules that physically allow repair of damaged tissue. They also operate on an independent circadian rhythm. Researchers from the British Medical Research Council Laboratory of Molecular Biology have shown that mice that sustained skin wounds during their active period had a stronger fibroblast response and healed more rapidly than animals that were injured during their sleep cycle. The authors noted that the animal data are in line with clinical observations that in humans, burn wounds sustained during daytime heal much more rapidly than those sustained at night. "The observation that wound healing is more efficient during the active phase could inform future clinical practice and has clear translational potential," the authors wrote. "We speculate that maximal healing could be promoted by pharmacological resetting of local cellular clocks before surgery, such as through topical application of chronoactive drugs." Their work appeared in the Nov. 8, 2017, issue of *Science Translational Medicine*.

Predicting pancreatic antitumor immunity

Pancreatic tumors are among the most lethal cancers, with five-year survival rates in the single digits. Those individuals that do survive are able to mount a T-cell response to the tumor, but the antigens that enable such a response have been unknown to date. Now, a team from Memorial Sloan-Kettering Cancer Center has analyzed the immune response of long-term survivors to understand how it protected them. They showed that while higher levels of tumor antigens were not protective by themselves, specific antigen characteristics, in particular a similarity of tumor antigens to microbial antigens, could predict survival. "Our results identify neoantigens with unique qualities as T-cell targets in pancreatic ductal adenocarcinoma," the authors wrote. "More broadly, we identify neoantigen quality as a biomarker for immunogenic tumors that may guide the application of immunotherapies." They published their findings in the Nov. 9, 2017, issue of *Nature*.

Helping the heart stay young, literally

"Understanding and modulating fetal-like genes in the failing heart may lead to potential diagnostic, prognostic, and therapeutic options in [heart failure]." That is the conclusion of researchers from the Dutch University of Groningen Medical Center. During heart failure, cardiac cells switch from the expression of adult genes to a more fetal-like gene expression pattern. The team screened for the genes that are turned on during that switch, and identified a previously unknown gene, OPLAH, whose expression had cardioprotective effects. The team showed that mice that overexpressed OPLAH had better cardiac function and reduced fibrosis after experimentally induced cardiac injury. The researchers concluded that "OPLAH is a potential target for therapeutic intervention in [heart failure]." They published their results in the Nov. 8, 2017, issue of *Science Translational Medicine*.

Stress resistance

Stress hormones cooperated with epidermal growth factor receptor (EGFR) tyrosine kinase signaling to enable resistance to EGFR inhibitors in cell culture and mouse models of non-small-cell lung cancer (NSCLC). EGFR inhibitors such as Gilotrif (afatinib, Boehringer Ingelheim GmbH) typically lead to spectacular but short-lived remissions, as tumor cells develop resistance. Scientists from MD Anderson Cancer Center investigated mechanisms of that resistance, and showed that stress hormones induced resistance by inactivating the tumor suppressor LKB-1 and inducing production of the cytokine IL-6. "These findings provide evidence that chronic stress hormones promote EGFR TKI resistance," the authors wrote, "and suggest that combinations of b-blockers with EGFR TKIs merit further investigation as a strategy to abrogate resistance." More generally, the work identified a mechanism of resistance that was not dependent on a mutation. Such mutation independent mechanisms of resistance are still mostly poorly understood. The results appeared in the Nov. 8, 2017, issue of *Science Translational Medicine*.

That's no virus

Heart attacks set off an antiviral immune response that further damages the heart, and interfering with that immune response improved survival in mice after an experimentally induced heart attack. Researchers at the Center for Systems Biology analyzed the molecular drivers of the inflammation that occurs after a heart attack. They showed that when cardiac cells died, the resulting debris was taken up by macrophages, setting of an interferon response. Blocking interferon production reduced the sequelae of heart disease, as did treatment with an antibody that blocked the interferon receptor. In mice the antibody was effective when given after an experimental heart attack. "We suggest that transient inhibition of the interferon-dependent innate immune response to ischemic cell death could reduce inflammation and limit the adverse ventricular remodeling that leads to clinical heart failure," the authors wrote. "Humans tolerate the anti-interferon biologics that are in clinical development for rheumatologic indications, suggesting the feasibility of targeting the interferon response in [heart attack]." They published their findings in the Nov. 6, 2017, issue of *Nature Medicine*.

Continues on next page

Bench Press

Continued from previous page

Asprosin is new hunger hormone

A recently identified hormone could be a therapeutic target in diabetes and obesity. Researchers from the Baylor College of Medicine identified the hormone, which is called asprosin, while studying the rare disorder neonatal progeroid syndrome (NPS). One of the symptoms of NPS is drastically reduced food intake, and the authors linked that to a lack of circulating asprosin, which is normally produced in response to fasting and activates both feeding circuits in the brain and energy production by the liver. In their new work, the authors demonstrated that treating mice with an antibody to asprosin reduced food intake and body weight. The authors argued that "pathologic elevation of asprosin in human insulin resistance and obesity, and the observed efficacy of immunologic neutralization of asprosin against insulin resistance and obesity in mice . . . suggest that pharmacological disruption of asprosin function could serve as a potentially unique therapeutic avenue against such diseases." Their work appeared in the Nov. 6, 2017, issue of *Nature Medicine*.

Cholesterol causes heart failure

Epidemiological evidence has strongly linked high cholesterol levels to heart failure, but a causal relationship has never been demonstrated. Now, a team from the Belgian Catholic University of Leuven has demonstrated such a causal relationship through gene therapy experiments in mice. The team used gene therapy to restore the low-density lipoprotein (LDL) cholesterol receptor to knockout mice lacking that receptor. The treatment reduced the levels of plasma cholesterol by about 80 percent. That cholesterol-lowering gene therapy also "attenuated cardiac hypertrophy, decreased interstitial fibrosis, counteracted metabolic remodeling, and lowered oxidative stress in mice with pressure overload. [Both] systolic and diastolic cardiac functions were improved." The team showed a beneficial effect both in healthy mice and in those with cardiac pressure overload, a condition that leads to heart failure. That work appeared in the Nov. 1, 2017, print edition of *Molecular Therapy*.

New protective mechanism in AD

The Sortilin-related receptor with LDLR class A repeats (SORLA) is a brain transport protein, and mutations that prevent it from carrying out its functions raise the levels of amyloid beta (a-beta), and the risk of Alzheimer's disease (AD). Previous research has established that SORLA worked in part by shuttling a-beta into lysosomes, where they were degraded. Researchers from the Sanford Burnham Prebys Medical Discovery Institute have identified an additional mechanism. The team showed that SORLA also inhibited EphA4, a receptor that binds to a-beta and mediates damage between neuronal connections. Transgenic mice expressing SORLA had less synaptic damage and less memory loss in response to high levels of a-beta than wild-type animals. The team concluded that "these findings provide a novel mechanism by which SORLA loss of function mutation significantly increases AD risk." The researchers published their results in the Nov. 7, 2017, issue of the *Journal of Experimental Medicine*.

AD drug works for fragile X

Treatment of fragile X mice with a drug in clinical development for Alzheimer's disease (AD) improved their symptoms, and the improvement lasted beyond the treatment itself. Fragile X is a neurodevelopmental disorder that results from a triplet expansion within the gene fragile X mental retardation 1 (FMR1). Its protein, the fragile X mental retardation protein (FMRP), is an RNA binding protein that affects many different RNAs. Overall, those effects alter synaptic function, and autism-like behaviors and mental retardation are core symptoms of fragile X. Researchers from Tetra Discovery Partners Inc. tested the experimental AD drug BPN-14770 because the drug inhibits phosphodiesterase-4 (PDE4), which previous research had implicated in fragile X. The team showed that treating FMR1 knockout mice with BPN-14770 daily for two weeks "reduced hyperarousal, improved social interaction, and improved natural behaviors such as nesting and marble burying as well as dendritic spine morphology," and that "the behavioral benefit of BPN-14770 persisted two weeks after washout of the drug," suggesting the drug has potential for the treatment of fragile X. The work appeared in the Nov. 7, 2017, issue of *Scientific Reports*.

Resveratrol rides again

Small-molecule analogues of resveratrol altered messenger RNA (mRNA) splicing and forestalled cellular senescence, researchers from the British University of Exeter and University of Brighton have reported. Resveratrol is a sirtuin activator that has received much attention for its purported anti-aging properties. The team investigated a role for resveratrol analogues in mRNA processing because previous work had suggested that altered processing underlies cellular senescence, and that resveratrol could affect such processing. The team showed that treating senescent cells with resveratrol was associated with altered splicing factor expression and rescue of multiple features of senescence, and caused the cells to re-enter the cell cycle. "This is the first demonstration that moderation of splicing factor levels is associated with reversal of cellular senescence in human primary fibroblasts," the authors wrote. "Small-molecule modulators of such targets may therefore represent promising novel anti-degenerative therapies." Their results were reported in the Oct. 17, 2017, issue of *BMC Cell Biology*.

Let us know what you think

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