TOGETHER AGAIN, AND SAILS-UP FOR COLUMBUS

Encorafenib encore in Array’s last BRAF laugh: On deck with MEK drug via deal with Novartis

By Randy Osborne, Staff Writer

Under a deal that depends on Novartis AG’s big, pending asset swap with Glaxosmithkline plc (GSK), the BRAF inhibitor encorafenib (also known as LGX818) – stranded with Novartis since December, when the pharma giant returned MEK blocker binimetinib rights to Array Biopharma Inc. – is joining its sister at Array, and the phase III combination trial called COLUMBUS in BRAF-positive melanoma (encorafenib’s fate in which had been unsure), will go on.

“From our perspective, these two products have great potential either separately or together,” said Brian Walker, Array’s chief medical officer.

FINANCINGS

Zafgen prices $138M offering to target obesity subpopulations

By Michael Fitzhugh, Staff Writer

Zafgen Inc.’s shares (NASDAQ:ZFGN) rose 5 percent to $38.97 Friday as the company priced a public offering of about 3.9 million shares at $35 each. The Boston-based company is raising $138 million.

See Zafgen, page 5

Progenics seeks new life for Azedra in ultra-orphan cancers

By Marie Powers, Staff Writer

After a delay of nearly five years, Progenics Pharmaceuticals Inc. dosed the first patient in a resumed phase II registration study of the radiotherapeutic Azedra (Ultradex iobenguane I 131). The drug’s original developer ran out of money in 2010 and was picked up in 2013 by Progenics. The trial, which is designed to treat patients with graft-versus-host disease (GvHD), is scheduled to enroll up to 24 patients.

See Progenics, page 4

EUROPE

Italian gene therapy start-up Genenta banks $7M in series A round

By Cormac Sheridan, Staff Writer

DUBLIN – Italian gene therapy pioneer Luigi Naldini is one of the co-founders of a new start-up, Genenta Science SpA, a spinout from the San Raffaele Hospital in Milan, which aims to exploit his deep expertise in transduction of immune cells.

See Genenta, page 6

NEWCO NEWS

Omni Bio chases chance to bring recombinant AAT to patients

By Michael Fitzhugh, Staff Writer

Riding high on new interim data suggesting plasma-derived alpha-1 antitrypsin (AAT) might help patients with graft-vs.-host disease (GvHD) recover when steroids fail, Omni Bio is chasing the chance to bring its recombinant AAT to market.

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BENCH PRESS

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

Read this week’s edition

CDX ALLOW MEDICINE TO GET PERSONAL

Companion diagnostics still serve as gatekeeper of personalized medicine

By Mark McCarty, Washington Editor, Medical Device Daily

A number of politicians, including President Obama, have jumped on the personalized medicine bandwagon,

See Companion, page 8
The EMA’s Committee for Medicinal Products for Human Use (CHMP) is recommending the suspension of hundreds of drugs being marketed in the EU that were approved based primarily on clinical studies conducted at GVK Biosciences in Hyderabad, India. Although there’s no evidence of harm or lack of effectiveness of the drugs, the recommendation is based on findings from a French inspection of the contract research organization last year that revealed data manipulations of electrocardiograms in nine studies of generic drugs over at least a five-year time period. “Their systematic nature, the extended period of time during which they took place and the number of members of staff involved cast doubt on the integrity of the way trials were performed at the site generally and on the reliability of data generated at that site,” the EMA said. In making the recommendation, CHMP looked at 1,000 pharmaceutical forms and strengths studied at the GVK site. It found sufficient supporting data from other sources for more than 300 of them, so those formulations will remain on the EU market. However, CHMP advises that the remaining products that lack data from other studies should be suspended unless they are critical drugs with insufficient alternatives to meet patients’ needs. The committee’s recommendation will be sent to the European Commission for a legally binding decision that would apply to all EU member states. While GVK said it is working with the EMA to resolve the issues, it called the recommendation “unprecedented and highly disproportional” as French authorities had noted that their findings should not be extrapolated to other trial-related activities at the clinical facility.

FINANCINGS

Alder Biopharmaceuticals Inc., of Bothell, Wash., said underwriters exercised in full their option to purchase 900,000 additional shares as part of its underwritten public offering, bringing gross proceeds from the offering to approximately $203.6 million. Credit Suisse, Leerink Partners and Wells Fargo Securities acted as joint book-running managers, with Sanford Bernstein as co-manager. On Friday, the company’s shares (NASDAQ:ALDR) fell $1.06 to close at $28.05. (See BioWorld Today, Jan. 9, 2015.)

Biomarin Pharmaceutical Inc., of San Rafael, Calif., said underwriters of its recent public offering exercised in full their option to purchase a about 1.2 million more shares at the offering price of $93.25 each. (See BioWorld Today, Jan. 23, 2015.)

Carbylan Therapeutics Inc., of Palo Alto, Calif., set terms for an initial public offering that would raise $75.4 million at the midpoint of its $12 to $14 range. Leerink Partners LLC, JMP Securities LLC and Wedbush Securities Inc. are underwriting the offering. The company, initially focused on osteoarthritic pain, granted them a 30-day option to purchase up to 870,000 additional shares. Proceeds will primarily support trials of Hydros-TA, the company’s intra-articular injectable candidate featuring cross-linked hyaluronic acid in the form of hydrogels, and working capital and other corporate purposes.

STOCK MOVERS 1/23/2014

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Biotechs showing significant stock changes Friday
Array

Continued from page 1

together,” Ron Squarer, CEO of Boulder, Colo.-based Array, said during a conference call with investors. Still, Array is “very pleased with the outcome” that did not leave them separated, he said.

Wall Street was, too. Shares of Array (NASDAQ: ARRY) closed Friday at $7.11, up $2.06, or 40.8 percent.

The binimetinib deal in December, which brought an $85 million payment from Basel, Switzerland-based Novartis, and the LGX818 arrangement, which involves only a small and undisclosed sum due from Array to Novartis, are contingent on the success of Novartis’ $26.6 billion transaction with GSK, of London, disclosed in April. (See BioWorld Today, April 23, 2014, and Dec. 5, 2014.)

“It’s critical for us to get to [closing of the Novartis/GSK pact],” Squarer explained. “We will have had an opportunity to fully understand the datasets” related to both compounds, and can “not only describe what our plans for these two agents would be going forward, but the plans for Array and its portfolio at the same time,” along with guidance “about where our cash position is, and how that cash would be deployed.”

If Array fails to find a European commercialization partner for LGX818 as well as binimetinib within a timeframe that has not been made public, a trustee will sell the European rights, but Array could get cash up front, milestone payments and royalties, Squarer said. “The period that we have to partner both of these assets in Europe is not public and won’t be public,” he said, but called the term “sufficient,” as long as “there is the kind of interest we would expect for this great combination, not to mention these two drugs separately that could be valuable on their own.”

A trustee, anyway, would be “trying to achieve the same goal ultimately that we would be attempting to achieve in the proscribed period,” Squarer said. The European Commission probably “has in its mind what [the best] partner would look like,” he said, but the regulators’ interest “is really no different” from Array’s.

‘HIGH LIKELIHOOD’ OF ON-TIME PARTNER

Meanwhile, Novartis has conceded to keep running COLUMBUS through June 2016 or until the end of patient visits, at which point Array will take over the study and be reimbursed by Novartis for half the costs. Novartis will supply encorafenib for clinical and commercial use for up to 30 months after closing and will also assist Array in the technology and manufacturing transfer of the compound, also providing Array continued access to pipeline compounds for use in currently ongoing combo studies – and potential future ones. “Based on these two agreements as they exist currently, we have no financial obligations to Novartis going forward in any scenario,” Squarer said.

Array is testing binimetinib as a single agent in phase III trials against low-grade serous ovarian cancer and NRAS-mutant melanoma.

NRAS cases make up about 20 percent of melanomas, Squarer said, and Array “expect[s] to be first and potentially alone in that indication for some time.” In ovarian cancer as well, the matter is “less of a differentiating question and more of a will-the-trial-be-successful” question, he said.

“The only competitive indication we’re pursuing is BRAF melanoma,” Squarer said, “knowing that we wouldn’t be first, because there’s the potential for differentiation,” specifically in tolerability with the MEK-BRAF combo. “On efficacy, it’s very difficult to predict what might come,” he said, though there’s “no reason to believe it would be any less effective” than other therapies, and the duration of effect is “quite substantial,” nine months to as long as a year.

“To have a regimen that is easier to live with, and to live well with, will be critical,” he said.

Andrew Robbins, senior vice president of commercial operations for Array, said the company does not expect to bring aboard any other of Novartis’ oncology candidates.

Wells Fargo analyst Matthew Andrews said the encorafenib news was “not entirely surprising,” since Array “has made it clear that it wanted to obtain the encorafenib rights, considering the phase I/II combination data in BRAF melanoma,” which represents twice the market opportunity as NRAS, along with the binimetinib combo potential, though it wasn’t certain under whose watch COLUMBUS might proceed.

“With 35 binimetinib and/or encorafenib studies under way, three pivotal registration studies ongoing (earliest data expected in the second half of this year in NRAS melanoma), and meaningful trailing support lowering overall development costs for Array and a future partner,” Andrews saw a “high likelihood” that the firm will sign a European partner before the clock runs out. In a research report, he maintained his “outperform” rating on the shares.

Edward Tenthoff, analyst with Piper Jaffray, viewed the latest headlines as “a positive surprise” and “another win” for Array. “With the $85 million from Novartis for the return of binimetinib, we estimate Array will hold pro forma cash of $216 million, and retains a $132 million convertible note due in 2020,” Tenthoff wrote in a research report, reiterating his “overweight” rating on Array with a $9 price target. //

OTHER NEWS TO NOTE

Celgene Corp., of Summit, N.J., said its Swiss subsidiary disclosed a positive opinion from the EMA’s Committee for Medicinal Products for Human Use for Abraxane (nab-paclitaxel) in combination with carboplatin for the first-line treatment of non-small-cell lung cancer in adult patients who are not candidates for potentially curative surgery and/or radiation therapy.
Progenics
Continued from page 1

being conducted under a special protocol assessment (SPA) with the FDA, is evaluating Azedra in patients with malignant pheochromocytoma and paraganglioma – rare neuroendocrine tumors that arise from cells of the sympathetic nervous system and have no approved antitumor treatments.

The move gives Tarrytown, N.Y.-based Progenics a second shot at cancer treatment, behind additional assets gained from its acquisition of Molecular Insight Pharmaceuticals Inc. (MIPI).

In its early years, Progenics focused solely on the development of Relistor (methylnaltrexone bromide), the opioid-induced constipation (OIC) drug for patients with advanced disease, which was partnered with Wyeth when it gained approval from the FDA in 2008. (See BioWorld Today, April 28, 2008.) When Wyeth and Pfizer Inc. merged in 2009, Progenics regained global rights to the drug in an amicable parting that included transitional support in the U.S. and abroad. In 2011, Progenics licensed rights to the drug to Salix Pharmaceuticals Ltd., of Raleigh, N.C., in a potential $350 million deal. (See BioWorld Today, Oct. 15, 2009, and Feb. 8, 2011.) Though it took some heavy regulatory lifting, that arrangement has been fruitful for both companies, with subcutaneous Relistor gaining a supplemental FDA approval last year to treat patients with chronic noncancer pain – an event that earned Progenics a $40 million milestone payment from Salix. (See BioWorld Today, July 15, 2014.) Salix has indicated that it expects to file the new drug application (NDA) for oral Relistor in the first half of this year.

Progenics grabbed MIPI, which had filed for Chapter 11 in 2010, in an all-stock deal designed to shift its pipeline in the direction of late-stage oncology diagnostic and small-molecule therapeutic candidates. The most attractive jewels in the transaction were MIPI’s prostate-specific membrane antigen (PSMA) assets, according to Progenics CEO Mark Baker. They included MIP-1404, a small molecule designed to diagnose and stage prostate cancer, and MIP-1095, a small molecule that binds to the extracellular domain of PSMA and is taken up by the cell before unleashing a payload of iodine-131 beta particles to kill the cancer.

Last year, Progenics reported data from a phase II study of MIP-1404 confirming uptake of 1404 in the lobes of the prostate gland and demonstrating the agent successfully detected metastatic prostate cancer in the lymph nodes. Although MIP-1095 completed multiple phase I studies, the company has not yet advanced it into phase II, according to Cortellis Clinical Trials Intelligence.

However, Progenics did complete a phase II trial of a PSMA antibody-drug conjugate in metastatic castration-resistant prostate cancer, giving the company multiple shots in that space.

“We’re looking to address not just therapy but also the important decisions that prostate cancer patients and their families face as they think about the treatment path,” Baker explained.

‘WE FEEL THE DRUG IS WELL-POSITIONED IN THIS CLINICAL TRIAL’
Azedra, which garnered the SPA all the way back in 2009, was something of an afterthought, Baker conceded. (See BioWorld Today, March 12, 2009.) “Once we analyzed the opportunity closely, we saw that the drug could provide great benefit to these patients with pheochromocytoma or paraganglioma, and we hopped on it,” he told BioWorld Today.

The phase II study was designed to evaluate the efficacy and safety of two therapeutic doses of Azedra in patients with malignant relapsed or refractory pheochromocytoma or paraganglioma, using a surrogate marker as a registration endpoint. MIPI suspended enrollment in 2010 while it sought additional funding. At the time, 41 patients had been treated, and initial data reported in 2012 showed that 32 percent of those achieved the primary endpoint of a reduction of at least 50 percent in the use of antihypertensive medication for at least six months.

The SPA requires that 25 percent of 58 evaluable patients achieve the primary endpoint. Based on guidance received from the FDA, Progenics expects to complete enrollment in the phase II this year and to report data in 2016, Baker said. If the findings achieve the approvable endpoint, the company plans to proceed directly to an NDA filing for Azedra, which has orphan drug and fast track designation from the FDA.

“We feel the drug is well-positioned in this clinical trial to achieve the patient enrollment we need, and we’re hoping the trial results meet the SPA endpoint,” Baker said.

To date, the most common adverse events observed with Azedra have been gastrointestinal disorders and thrombocytopenia.

In September 2014, when Progenics presented long-term follow-up data on the previous 41 patients treated in the phase II trial, Brean Capital LLC analyst Jonathan Aschoff predicted “equally robust data from the next 17 patients.” Progenics will seek first approval in the U.S. but is looking eventually to partner Azedra in other regions. At the International Symposium on Pheochromocytoma and Paraganglioma, held in September 2014 in Kyoto, Japan, “we learned a lot about how pheo is seen throughout the world,” Baker said, “so we’re definitely thinking broader.”

Jefferies Group LLC analyst Ryan Martins pegged Azedra at approximately $61 million in peak U.S. sales in the indications. In addition to potential global sales, a bigger win for the drug could be in neuroblastoma and other neuroendocrine diseases, where Azedra showed promise in small proof-of-concept studies.

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Zafgen

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million to advance development of beloranib as a treatment for obesity and hyperphagia in Prader-Willi syndrome (PWS) patients as well as hypothalamic injury-associated obesity (HIAO).

The deal’s underwriters have an option to purchase up to an additional 514,200 shares of common stock at $35 each. The offering is expected to close on or about Jan. 28.

Leerink Partners LLC and Cowen and Co. LLC are acting as joint book-running managers for the offering. Canaccord Genuity Inc. and JMP Securities LLC are acting as co-managers.

In addition to targeting severe obesity in PWS and HIAO patients, beloranib, a twice-weekly subcutaneous injection, is being developed for the treatment of craniopharyngioma-associated obesity.

The company is taking a step-wise approach it developed a year ago while still a privately funded company and staring down the challenge of attacking obesity head-on, CEO Tom Hughes told BioWorld Today.

It’s first advancing beloranib in subpopulations of obese patients, including those with rare conditions where obesity is a co-morbidity. The point is to find a streamlined path to registration with smaller patient populations and, accordingly, lower-cost trials.

Little more than six months after the company’s successful initial public offering, the methionine aminopeptidase 2a (MetAP2) inhibitor met the primary efficacy endpoint of weight reduction in a small phase II trial in patients with HIAO and is being tested in a phase Ib study for the treatment of patients with both severe obesity and type 2 diabetes. (See BioWorld Today, Jan. 8, 2015.)

Proceeds from the follow-on will help the company advance beloranib as a treatment for obesity and hyperphagia in PWS patients by completing two phase III studies; help kick off work to extend those indications to pediatric patients; and bring plans to use the drug in HIAO closer to the finish line by funding two pivotal phase III studies.

The money will also help Zafgen finish investigational new drug application-enabling studies and phase I development of another drug, ZCN-839, for nonalcoholic steatohepatitis and support the company’s ongoing work to develop beloranib back-ups or follow-on molecules for severe obesity in the general population, including a next-generation MetAP2 inhibitor currently in preclinical development.

“There’s a high level of awareness within the investment community of the importance of obesity as a health care issue,” Hughes said. “They recognize that this is one of the next major untapped markets for therapeutics that has been frustrating in terms of the performance of compounds and devices that have come out.

“I think it’s clear that there’s a way to crack this, but it hasn’t been shown yet by any of the agents that are out there,” he said.

There has been progress. In the U.S., the FDA has approved Vivus Inc.’s Qsymia (phentermine/topiramate), Arena Pharmaceuticals Inc.’s Belviq (lorcaserin), Orexigen Therapeutics Inc.’s Contrave (naltrexone and bupropion) and, more recently, the Novo Nordisk A/S drug Saxenda (liraglutide). (See BioWorld Today, Sept. 12, 2014.)

That has shown that the FDA is “certainly open for business” when it comes to approving obesity treatments, said Hughes.

What’s still needed though, he added, is a medication that leads to weight loss that’s both “meaningful to patients and medically relevant, and therefore of interest to physicians and payers.”

RBC Capital Markets LLC analyst Simos Simeonidis initiated coverage of the company Thursday with an “outperform” rating and a $53 price target, modeling peak combined U.S. and EU sales of beloranib in PWS and HIAO of $750 million and $630 million, respectively.

“Early studies of injectable agent beloranib in obese patients resulted in impressive weight loss,” Simeonidis wrote. He said two factors make beloranib’s efficacy impressive: First, “it was achieved without the benefit of any diet or exercise.” Second, he said, weight loss didn’t seem to plateau after 12 weeks of treatment, “suggesting that even more weight loss could be achieved with longer treatment.”

Phase III data for beloranib in PWS is expected by year’s end. //

FINANCINGS

Otonomy Inc., of San Diego, priced its follow-on public offering of 2.55 million common shares at $29.25 apiece for gross proceeds of approximately $75 million. The company granted the underwriters a 30-day option to purchase up to 382,500 additional common shares, potentially generating another $11.2 million. In its registration statement, Otonomy said proceeds will be used to fund activities related to U.S. regulatory approval and commercialization of lead candidate Auripro (formerly OTO-201), a sustained-exposure version of the antibiotic ciprofloxacin. The company also plans to conduct trials for Auripro in one or more potential expansion indications. Funding also will be used to move OTO-104, a sustained-exposure formulation of the steroid dexamethasone, into clinical development and potentially through a phase III trial and to complete preclinical development and conduct a phase I trial of OTO-311, a sustained-exposure formulation of N-methyl-D-aspartate receptor antagonist gacyclidine. The offering is expected to close Jan. 28. J.P. Morgan Securities LLC is acting as sole bookrunner, with Piper Jaffray & Co. and Cowen and Co. LLC as lead managers and Sanford C. Bernstein & Co. LLC as co-manager. Otonomy completed its initial public offering in August 2014, pricing at $16 and raising $100 million. On Friday, the company’s shares (NASDAQ:OTIC) gained $3.59, or 12.2 percent, to close at $32.93. (See BioWorld Today, Aug. 14, 2014.)
Genenta  
Continued from page 1

experience in lentiviral vectors in the development of ex vivo engineered autologous cell therapies for cancer.

Milan-based Genenta has raised €6.2 million (US$7 million) in a first closing of its series A round. Co-founder and company chairman and CEO Pierluigi Paracchi told BioWorld Today that it has received commitments that will take the total to €10 million in the coming weeks.

Paracchi, a venture capital investor, was associated with a recent Italian biotech success, the sale of Ethical Oncology Science SpA (EOS) to Clovis Oncology Inc., of Boulder, CO, in a deal worth $200 million up front and as much as $420 million eventually. (See BioWorld Today, Nov. 21, 2013).

The third member of the founding team, Bernhard Gentner, is a physician scientist, who, like Naldini, is also based at the San Raffaele Hospital. He also holds a position at the San Raffaele-Telethon Institute for Gene Therapy, of which Naldini is director.

The cash injection will enable the company to complete ongoing preclinical development work and to initiate phase I trials in patients. “Also, during the preclinical development period we will prepare and organize our manufacturing activities,” Paracchi said. “Our idea is to enter the clinical phase between the end of 2016 and the beginning of 2017.”

Genenta is recasting an old idea in a modern guise. It aims to arm tumor-infiltrating lymphocytes with interferon-alpha (IFN-alpha), a cytokine involved in host defense against viral pathogens, which also has antitumor activity. Until recently a cornerstone of therapy for hepatitis C virus infection, IFN-alpha has not been widely used in cancer therapy because of the levels of toxicity associated with an effective dose.

Naldini and colleagues previously identified a Trojan horse – a population of monocytes that expresses a tunica interna endothelial 2 (TIE2) receptor tyrosine kinase, which binds angiopoietin growth factor and helps to regulate the maturation and stabilization of blood vessels. Expression of the TIE2 gene is sharply up-regulated once those cells infiltrate tumors, and it leads to both pro-angiogenic and immunosuppressive effects.

Genenta's approach is based on turning those monocytes into carriers of a gene encoding IFN-alpha. To minimize any potential systemic effects, the gene is placed under the transcriptional control of the TIE2 promoter and also under the post-transcriptional control of a microRNA species. That ensures that expression is conditional and largely confined to the tumor microenvironment.

Genenta's lead indication will be multiple myeloma patients undergoing bone marrow transplant. “It's crucial for us to work with hematopoietic stem cells,” Paracchi said.

The basic approach is described in a paper, which was published online on April 29, 2014, in Oncoimmunology, under the title “Engineered tumor-infiltrating macrophages as gene delivery vehicles for interferon-α activates (sic) immunity and inhibits (sic) breast cancer progression.”

The company is building on Naldini's two decades of involvement at the forefront of gene therapy. During the mid-1990s, he pioneered the development of lentiviral vectors in nonreplicating cells while working with Inder Verma at the Salk Institute, of La Jolla, Calif. More recently, he has harnessed those to correct the hematopoietic stem cell genotypes of patients with rare genetic conditions such as metachromatic leukodystrophy and Wiskott Aldrich syndrome.

A syndicate of private investors, family offices and high net worth individuals have backed the company. Its board includes Roger Abravanel, also a director of Teva Pharmaceutical Industries Ltd., of Petach Tikva, Israel, and EOS co-founder Gabriella Camboni, who is also on the investment team of Ares Life Sciences, the investment arm of the Bertarelli family. //
Omni
Continued from page 1

Pharmaceutical Inc. is angling to produce an irresistible proof-of-concept package showing its preclinical recombinant AAT (rAAT) could do the same and more.

The phase I/II GvHD data, produced by its academic collaborators at the University of Washington and the Fred Hutchinson Cancer Research Center and presented at December’s American Society of Hematology meeting, showed that just eight intravenous (I.V.) doses of plasma-derived AAT helped reduce inflammation and promote healing of damaged tissues in a small group of patients (five of seven) who developed severe acute GvHD after undergoing bone marrow transplants. Though the data are early, Omni Bio said it believes those results point to the potential for its rAAT therapy to offer similar benefits.

About 40,000 bone marrow transplants are done in the U.S. and Europe every year. At least half of those patients develop GvHD. And about half of those GvHD patients don’t respond to high-dose steroid therapy. Steroid refractory GvHD patients often develop severe diarrhea and can die within three to nine months.

Because of its anti-inflammatory and tissue protective effects, many of those patients are treated with AAT. But while there are four FDA-approved forms of plasma-derived forms of ATT, including Prolastin-C (Grifols SA) and Glassia (Kamada Ltd.), making them requires harvesting donor blood, purifying it and following other complex procedures.

Costs are also an issue. Estimated mean annual costs for patients receiving augmentation therapy are up to approximately $80,000 per year, according to Wolters Kluwer UpToDate. A recombinant formulation could potentially be more “economically viable,” according to Omni Bio CEO Bruce Schneider.

Omni Bio was originally formed to monetize method-of-use patents it holds on plasma-derived AAT. It joined the OTC market in 2009 to raise funds to support proof-of-concept studies intended to demonstrate that AAT could be beneficial in type 1 diabetes and elsewhere. While the strategy turned out to be less viable than first thought, it did help clarify the advantages recombinant AAT may offer.

The company now sees a broad opportunity for its rATT molecule, from applications in GvHD to type 1 diabetes and chronic gout – areas in which Schneider told BioWorld Today he believes the company can produce crisper phase Ila proof-of-concept data, setting the stage for an eventual exit.

“We think that if you can do the proper studies, or if a partner can help us do the proper studies, we should be looking at a fast track through a regulatory approval and a fairly fast approach to market with an orphan drug designation in GvHD,” he said.

It’s possible that if rAAT worked in treatment, it could even one day be used prophylactically to treat all bone marrow transplant patients or even lead to the possibility of relaxing matching criteria for donors, such that it would possible for patients not currently eligible for transplants to receive them, Schneider said, pointing out that the probability of mismatches is substantially higher in certain non-white patients than it is in white patients.

Early scientific investigations have shown rAAT to be 40 times to 50 times more potent that the plasma-derived form. Though it’s not clear why that is, Schneider said, the purification process may be the cause. Regardless, he said, “if we could give 1/50th the dose and achieve the same biological effect, we think that instead of giving the drug intravenously, which is how it’s given now, we could give it subcutaneously, which would be a huge benefit for patients.”

In type 1 diabetes, three pilot studies to date have shown plasma-derived AAT can deliver a flattening in the loss of beta cell function, leading to two of the four manufacturers of plasma-derived AAT, Grifols and Kamada, to pursue pivotal phase II/III studies in type 1 diabetes. Further clinical findings have shown a single dose of plasma-derived AAT can blunt post-heart attack inflammation.

“We hope to ride on the coattails of the clinical findings with the plasma drug as we develop our recombinant drug,” said Schneider. “We think that de-risks our opportunity going forward.”

LOOKING FOR INVESTORS, PARTNERS

The company is incorporated in Fort Collins, Colo., near the source of its technology, the University of Colorado, Denver. But like many small modern biotechs, it operates as a virtual venture, with just six full-time employees, including Schneider and Chief Financial Officer Jack Riccardi working out of Pennsylvania.

Schneider’s background is in big pharma, having served as an executive at Wyeth Research and later at Pfizer Inc. A friend from those days turned him on to the early scientific work that formed the basis for AAT-Fc, the recombinant form of AAT that consists of a proprietary Fc-fusion construct that’s similar in design to the blockbuster drug Enbrel (etanercept, Amgen Inc.), which he worked on with Immunex Corp. during his tenure at Wyeth.

Given the company’s potential, Schneider thought it would be fairly easy to advance the project. Funding for promising R&D projects appeared more or less at the snap of the fingers in his big pharma days, he said. Though laying the groundwork for success at a small company has been quite a bit more work than he first anticipated, he and his team have already made significant progress.

So far, the company has created an economically feasible level of cell line expression, with clones on hand that make the project commercially viable. It has also confirmed that it can readily express recombinant AAT in Chinese hamster ovary cells, which are often used in both R&D and commercial production of biologics.
Companion
Continued from page 1
which a skeptic might say is a sure sign the idea will soon find itself mired in turf wars and ideological scrums. Regardless of the politics of personalized medicine, companion diagnostics (CDx) face several issues before they will have an impact on the practice of medicine, including FDA regulations, intellectual property issues and the existing framework for coverage and reimbursement of those tests. Until those issues are resolved, the CDx will continue to play the role of the rate-limiting component for a true 21st century approach to patient care.

At first glance, it appears some of those issues are at least several years away from resolution, which if true indicates the future is clearly not yet now. A strange measure of consolation can be had with the realization that the high cost of drug development ensures that CDx will remain a hot topic for at least a decade, possibly far longer.

The second and third entries in this three-part series on CDx will tackle intellectual property/patent considerations, and the twin issues of coverage and reimbursement. This first installment will look at the regulatory end of those tests, which may ultimately prove to be the least nettlesome part of the task of moving the practice of medicine into the 21st century.

Brad Thompson, a regulatory attorney with Epstein Becker Green (EBG) in Washington, discussed the FDA’s final guidance for CDx with Medical Device Daily, the introduction to which states that its provisions apply to drugs for which a CDx “is essential for the therapeutic product’s safe and effective use,” which might strike some as a bit elastic. Thompson said the language does leave the agency some leeway, but seemed unconcerned.

“Words are inherently subject to interpretation,” Thompson remarked, but he nonetheless said the FDA provided “a tightly worded definition” and set “a pretty high bar” for determining the need for a companion diagnostic.

“I don’t think [the] FDA has any intention of requiring a CDx with a drug” simply because a CDx could be used, Thompson said, but added that the agency would almost certainly require it “if the drug is at all serious in terms of its risk profile.” Thompson acknowledged that the question of a CDx requirement might in some instances seem to stray into regulatory overkill, but he added, “it will depend on the risk profile of the drug.” He pointed out, for example, that blood thinners are difficult to manage, “so some measurement is appropriate. In those cases, the measurement is pretty generic,” however, and should not require a formal CDx.

The CDx final seems to hint at a belief that a CDx would be a high-risk diagnostic in most cases and hence require a premarket approval application (PMA). Thompson remarked, “I think the majority of diagnostics manufacturers understand and appreciate that when the diagnostic is used to guide the decision-making around” a high-risk pharmaceutical agent, “that necessarily elevates the risk profile of the diagnostic.” He said many CDx filings will fall into class III, based principally or entirely on the risks associated with the use of the drug.

However, the expense associated with a PMA path does not necessarily rule out a small company’s entry. “If the drug company understands this is the only way they’re going to get approved, they have a pretty big incentive” to aid in the effort to develop a CDx, even if it means working with a smaller company.

The guidance mentions the possibility of running a single trial for both the drug and the diagnostic, but Thompson said, “from what I hear, it is difficult to test two hypotheses in the same trial” because such a practice is a case of “compounding what you don’t know.” The notion of a single trial for both products is attractive because firms are interested in “anything that can be done to bring down the cost” of development, Thompson pointed out. He remarked, however, that should such a model prove at all practical, “I’m sure companies would be all over it.”

SEPARATE APPLICATIONS
The FDA indicated it intends to evaluate a therapeutic and diagnostic as separate applications even when the pairing is clearly a combination product. Thompson said that did not surprise him. He stated that integral combination products such as drug-eluting stents are reviewed as single applications, but that cross-labeled products, which are made and sold separately and have separate instructions for use, are not handled the same. The “FDA has always treated cross-labeled combination products as two separate entities that require parallel reviews” from the respective centers at the FDA, he said.

James Boiani, also of EBG, told Medical Device Daily, “the guidance itself is helpful in clarifying the issues, but I think it leaves a lot of questions unanswerable as to how you get some of these approved.” He said the data requirements are not well described, and the regulatory end of the companion diagnostic will remain incomplete until the FDA issues a co-development guidance, which hopefully will lend some clarity as to how sponsors can develop therapies and associated diagnostics on parallel tracks.

“I know [the] FDA has been working on a co-development guidance,” Boiani said, adding that document is “still in process, which it has been for a long time.” He said the co-development guidance should spell out the agency’s “expectations in terms of developing clinical trials” such as the number of subjects enrolled and the number of samples. The document should also discuss “how you will actually deal with situations such as when the drug is on the market and you want to bring a CDx” to market after approval of the drug. In that latter scenario, there is no co-development and, in all likelihood, “you don’t have access to all the samples” used to develop the drug, which may prove to be a showstopper for development of the CDx.

“If [the] FDA has approved a drug broadly” and the sponsor of that drug wants a CDx, “there’s not a lot of incentive

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Omni

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To date, Schneider said he believes Omni Bio is the only company that has succeeded in creating rAAT. Prior attempts to make it over the last 20 years have all failed, he said, with no one able to come up with a version that was pharmaceutically appropriate, always running into problems such as short half-life, aggregation issues, folding, stability and other stumbling blocks.

Omni Bio’s chief scientific officer, Charles Dinarello, the University of Colorado professor who discovered interleukin-1 with colleagues, tried a different tack, using an Fc-fusion protein that’s able to be expressed by CHO cells “very consistently and very smoothly,” said Schneider.

To date, the company has raised about $10 million. Most of that has been devoted to advancing the recombinant molecule. Now it’s enlisting life sciences-focused banks to raise money from a broader group of investors, at the same time it looks for a potential strategic partner. The company is seeking $5 million to $6 million now to complete its preclinical development program; it is looking to raise an additional $2 million to $3 million in 2016 to support its first phase I studies; another $6 million would be needed in 2017 to conduct its first phase IIa proof-of-concept study in either type 1 diabetes, GvHD or gout. It’s also beginning to reach out to big pharma companies to explore the potential for a research collaboration, co-development arrangement or even a licensing agreement, Schneider said.

Meanwhile, it’s advancing characterization work, fine-tuning its process development, with hopes of taking it into animal toxicity studies by this summer. If all goes well, the molecule could be in human testing in mid-2016. //

Companion

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[for the drug sponsor] to do a lot of studies” to support a diagnostic, Boiani mused. A test maker might have an incentive “depending on how broadly the drug is used. Figuring out a way to deal with that kind of issue is what the co-development guidance will want to address,” he said.

“You want to encourage development and the agency needs to find a way to incentivize that,” Boiani added.

‘AN ISSUE OF COORDINATION’

“One issue that’s been somewhat controversial is that FDA seems to be saying . . . it doesn’t want any test trade name to be used in the [drug] label,” so as to encourage other test development, Boiani remarked, adding, “I’m agnostic on the issue, but some companies will want to have their trade name on the labeling.”

Assuming the sponsor of the therapeutic wants to allow an alternative test to be used for the therapeutic, there may be an issue with how the sponsor would deal with the drug’s label.

“There’s a question of whether the manufacturer wants to amend the label,” Boiani observed. He pointed out that there are some relatively efficient means of doing so. “If they did want to bring a new test to the label, I’d say that it seems like something you should be able to do with a CBE-30,” he said in reference to the 30-day changes-being-effected mechanism, or some similarly abbreviated path.

Another potential sore spot is the overlapping jurisdiction between the FDA and the Centers for Medicare & Medicaid Services (CMS), where lab testing is concerned, thanks in part to the FDA’s designs on regulation of lab-developed tests. “One of the problems some [developers] have had . . . is CMS getting involved in the regulations of these investigational products,” Boiani said. CMS may start flexing its regulatory muscle under the Clinical Laboratory Improvement Amendments (CLIA) and request validation of a test under that framework.

“I think it’s an issue of coordination,” Boiani said, which will prove essential in some states, such as New York, which have their own regulatory schemes for clinical labs. CMS engages third parties to certify labs, such as the College of American Pathologists in Northfield, Ill., but those organizations have even fewer ties to the FDA than CMS, making effective coordination an unlikely prospect as matters stand.

“What would be ideal . . . is to have some sort of mechanism” between the FDA and CMS that requires the FDA to notify CMS when it has issued an investigational device exemption (IDE) to a lab explaining the provisions of the IDE, Boiani said. He did not sound entirely optimistic on that score, however.

“Even though CMS and FDA are both under HHS, they don’t necessarily have those mechanisms in place.”

However, resolution of that and other issues is essential. The “FDA and CMS have worked together in the past,” Boiani said, adding, “if you want to add more incentive for development of CDx, you have to develop an efficient system” for the FDA’s review so that a coverage analysis commences when the FDA approves the CDx. //


FINANCINGS

Puma Biotechnology Inc., of Los Angeles, said underwriters exercised in full their option to purchase up to 150,000 additional common shares as overallotments in its underwritten public offering of 1 million shares priced at $190 apiece. Closing for the additional shares, which generated proceeds of $28.5 million, is expected to occur concurrently with the initial purchase on Jan. 27. BoF A Merrill Lynch and J.P. Morgan Securities LLC are acting as lead bookrunners, with Citigroup Global Markets Inc. as joint bookrunner. Leerink LLC and Cowen and Co. LLC are acting as co-managers. On Friday, the company’s shares (NASDAQ:PBVI) gained $18.17, or 9.3 percent, to close at $212.69. (See BioWorld Today, Jan. 23, 2015.)
Progenics
Continued from page 4

Thanks to the Relistor milestone payment and a growing royalty stream, Progenics doesn’t have near-term plans to raise money, according to Baker. The company ended the third quarter of 2014 with $87.4 million in cash, excluding the Relistor milestone.

“We’ve got a strong bank account and a lot of runway so, for the moment, we’re feeling good about our financial position,” he said.

And, although Progenics is paying close attention to its pipeline, the company is not above making opportunistic deals.

“We continue to look for late-stage oncology assets,” Baker said. “We’re particularly interested in assets that have been de-risked in some way, either through an SPA, as was the case with Azedra, or through proof-of-concept data or alternatives to overall survival endpoints.”

On Friday, the company’s shares (NASDAQ:PGNX) lost 4 cents to close at $6.14. //

OTHER NEWS TO NOTE

Immune Therapeutics Inc., of Orlando, Fla., said it signed a deal with compounding company KRS Global Biotechnology Inc. for the packaging and distributing of its naltrexone tablets. Terms were not disclosed. Immune Therapeutics has rights to low-dose naltrexone in several indications, including Crohn’s disease, inflammatory diseases, prostate cancer and lymph proliferative syndrome.

Incyte Corp., of Wilmington, Del., said it earned a $25 million milestone from Novartis AG, of Basel, Switzerland, triggered by the EMA’s positive opinion of Jakavi (ruxolitinib) for the treatment of adult patients with polycythemia vera (PV) who are resistant to or intolerant of hydroxyurea. Incyte expects to record that milestone as contract revenue, and receive the $25 million payment this quarter. The JAK1/JAK2 inhibitor previously gained FDA approval in PV patients. The drug is marketed in the U.S. as Jakafi.

Kythera Biopharmaceuticals Inc., of Westlake Village, Calif., said the FDA’s Dermatology and Ophthalmic Drugs Advisory Committee is scheduled to review the firm’s new drug application for ATX-101 (deoxycholic acid) for improvement in the appearance of moderate to severe submental fullness in a half-day meeting on the morning of March 9. ATX-101 has a PDUFA date of May 13.

Nanoviricides Inc., of West Haven, Conn., reported preclinical data showing that an optimized Flucide candidate demonstrated a good safety profile in a GLP-like toxicology study in rats. No direct adverse clinical effects were found upon administration of the Flucide candidate intravenously at doses of up to 300 mg/kg/day for 14 days, and there were no adverse histological findings in gross organ level histological examination, nor were there any adverse findings in microscopic histological analysis. Data also showed no meaningful effects observed on animal weight gain, food consumption, hematology or clinical chemistry at the end of the 14-day dosing period.

Regeneron Pharmaceuticals Inc., of Tarrytown, N.Y., said Eylea (aflibercept) injection was recommended for approval by the EMA’s Committee for Medicinal Products for Human Use for the treatment of visual impairment due to macular edema secondary to central or branch retinal vein occlusion. Partner Bayer AG, of Leverkusen, Germany, has exclusive marketing rights for Eylea outside the U.S. and Japan.

Restogenex Corp., of Buffalo Grove, Ill., presented data at the Keystone Symposia Series on PI 3-Kinase (PI3K) Signaling Pathways in Vancouver, British Columbia, showing that RES-529, its TORC1/TORC2 allosteric dissociative PI3K inhibitor in development for glioblastoma multiforme, demonstrated an ability to inhibit signal transducers of the PI3K pathway that are controlled by TORC1 and TORC2. That mechanism was shown in a variety of tumor cells, including cells that have lost tumor suppressor PTEN. In a second study, RES-529 was compared with two catalytic inhibitors of the PI3K pathway currently in the clinic and showed a 20-fold to more than 100-fold increase in activity above the other inhibitors. A third study demonstrated RES-529 penetrates the blood-brain barrier.

The Medicines Co., of Parsippany, N.J., said the EMA’s Committee for Medicinal Products for Human Use issued positive opinions recommending marketing authorization for three of its pipeline development candidates: Kengreal (cangrelor), an intravenous antiplatelet agent designed to provide immediate, consistent and rapidly reversible P2Y12 inhibition; Orabant (oritavancin), a single-dose antibiotic treatment for acute bacterial skin and skin structure infections caused by susceptible designated gram-positive bacteria; and Raplixa (sealant powder), a ready-to-use, biologically active, powdered fibrin sealant that provides hemostasis in a wide range of bleeding settings.

FINANCINGS

Verastem Inc., of Boston, saw its shares (NASDAQ:VSTM) rise 58 cents, or 8.3 percent, to $7.58, as it priced an offering of about 7.3 million shares slated to raise net proceeds of about $44.1 million. The offering is expected to close on or about Jan. 28. Jefferies LLC and Leerink Partners LLC are acting as joint book-running managers and Guggenheim Securities LLC and Oppenheimer & Co. Inc. are acting as co-lead managers. Verastem granted the underwriters a 30-day option to purchase up to about 1.1 million additional shares of common stock. The company plans to use the new funds to support its registration-directed COMMAND study in mesothelioma; the initiation of associated studies in preparation for a possible new drug application filing to the FDA and similar filings to other regulators; its other ongoing trials with VS-6063, VS-4718 and VS-5584; and for other general corporate purposes.


**FINANCINGS**

**Vitae Pharmaceuticals Inc.**, of Fort Washington, Pa., saw shares rise $2.42, or 20.2 percent, to $14.41 Friday as it priced a 3-million share follow-on offering at $11.90 per share to raise $35.7 million. The company also granted the underwriters a 30-day option to purchase up to an additional 450,000 shares of common stock. The offering is expected to close on or about Jan. 28. Stifel, BMO Capital Markets and Piper Jaffray & Co. are acting as joint book-running managers and JMP Securities and Wedbush Pacgrow Life Sciences are acting as co-managers.

Vitae is advancing a treatment of type 2 diabetes as well as an experimental Alzheimer’s disease therapy with partner **Boehringer Ingelheim GmbH**, of Ingelheim, Germany. (See *BioWorld Today*, Oct. 27, 2014.)

**IN THE CLINIC**

**Gem Pharmaceuticals Inc.**, of Birmingham, Ala., said the first soft-tissue sarcoma patients have been enrolled into the company’s phase II trial to assess the efficacy and safety of lead compound GPX-150 in about 30 adults as first-line therapy for advanced or metastatic disease. GPX-150 is an analogue of doxorubicin, modified at two locations in an effort to decrease the cardiotoxic side effect that limits the maximum cumulative dose of doxorubicin that can be safely administered, the company said.

**Lixte Biotechnology Holdings Inc.**, of East Setauket, N. Y., said the number of clinical sites where its phase I trial of lead compound, phosphatase inhibitor LB-100 for use in combination with docetaxel, is being conducted has been expanded from one to five institutions.

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**PHARMA: OTHER NEWS TO NOTE**

**Eisai Co., Ltd.**, of Tokyo, said the German Federal Joint Committee (G-BA) has confirmed that the largest defined patient group has “considerable” additional benefit of Halaven (eribulin) vs. certain comparator therapies as determined by the G-BA. Eribulin is approved for the treatment of women with locally advanced or metastatic breast cancer who have progressed after at least one chemotherapeutic regimen for advanced disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting, unless patients were not suitable for those treatments. The reassessment for eribulin is based on clinical evidence derived from two global phase III trials; EMBRACE (Eisai Metastatic Breast Cancer Study Assessing Treatment of Physician’s Choice Versus E7389, or Study 305) and Study 301 involving more than 1,800 women. In line with the G-BA requirements, additional pooled analyses of data were specifically performed for the benefit assessment procedure in Germany.

**Bayer AG**, of Leverkusen, Germany, said the National Institute for Health and Care Excellence issued its final appraisal determination recommending Xarelto (rivaroxaban) 2.5 mg twice daily as an effective treatment option for preventing secondary events – death, heart attack or stroke – following acute coronary syndrome in patients with elevated cardiac biomarkers, without prior stroke or transient ischaemic attack.

**Merck & Co. Inc.**, of Whitehouse Station, N.J., said in connection with the completion of the acquisition of Lexington, Mass.-based **Cubist Pharmaceuticals Inc.** it has commenced a tender offer to repurchase, at the option of each holder, any and all of its outstanding 2.50 percent convertible senior notes due 2017, 1.125 percent convertible senior notes due 2018 and 1.875 percent convertible senior notes due 2020. Merck completed the tender offer for all of the outstanding shares of common stock of Cubist, consummated the merger of Cubist into Mavec Corp. Inc., a wholly owned subsidiary of Merck, and terminated trading of Cubist’s common stock on the Nasdaq Global Select Market. (See *BioWorld Today*, Dec. 9, 2014.)

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Targeting yesterday’s Ebola?

Researchers from the U.S. Army Medical Research Institute of Infectious Diseases have reported that the Ebola virus behind the current outbreak may be mutating in a way that makes it less susceptible to several experimental drugs that are currently in development. The therapeutics currently under development were developed against older variants of the Ebola virus that caused outbreaks in the Democratic Republic of Congo in 1976 and 1995, respectively. Although the drugs were optimized to be broad spectrum and have shown activity against the strain behind the current outbreak, that strain has now also been circulating for long enough to undergo genetic changes. In their study, the authors looked at publicly available sequencing data for the current strain, and found that there are variants circulating that have mutations in many of the sites targeted by current experimental drugs. The authors noted that their study had a number of caveats, including the fact that changed binding does not necessarily influence therapeutic efficacy and that some of the experimental drugs “have been deliberately designed to be tolerant to possible target mutations.” Nevertheless, they warned that the efficacy of experimental Ebola therapeutics should be tested against the currently circulating strain, that a broad approach targeting multiple sites of the virus should be pursued for the best chances at success and that “given the ongoing continued person-to-person transmission, it is imperative that more current isolates be sequenced and evaluated in a similar manner.” Their work appeared in the online journal mbio on Jan. 20, 2015.

HIV co-opts B cells’ living quarters

Researchers at Oregon Health & Science University have identified one hiding place for HIV that keeps even elite controllers from eliminating the virus altogether. Elite controllers are individuals who are infected with HIV, but who do not progress clinically to AIDS. Nevertheless, such individuals also do not manage to rid themselves of HIV altogether, and HIV is replicating and evolving in elite controllers, showing that their reservoirs cannot consist only of nondividing T cells. In their work, the team showed that HIV was also present in B-cell follicles in primates that were elite controllers of HIV’s monkey equivalent, SIV. Those follicles, which are part of the B-cell generating germinal centers of the lymph system, prevent T cells from entering, thus providing a hiding place for HIV. The authors concluded that “B-cell follicles constitute ‘sanctuaries’ for persistent SIV replication in the presence of potent antiviral... T-cell responses, potentially complicating efforts to cure HIV infection with therapeutic vaccination or T-cell immunotherapy.” Their findings appeared in the Jan. 19, 2015, issue of Nature Medicine.

Novel psychiatric risk genes

The multi-institutional Psychiatric Genomics Consortium, led by scientists from the British King’s College London and the University of Cardiff, have conducted a genomewide association study (GWAS) on more than 60,000 individuals to find pathways whose malfunction plays a role in the three major psychiatric disorders of major depression, bipolar disorder and schizophrenia. Previous GWAS research has implicated multiple individual genes in those disorders, but those genes had not been linked into a coherent network. In their work, the authors developed bioinformatics methods that could identify such links, and they found that three pathways were most commonly affected in the individuals they studied. “Histone methylation processes showed the strongest association, and we also found statistically significant evidence for associations with multiple immune and neuronal signaling pathways and with the postsynaptic density. Our study indicates that risk variants for psychiatric disorders aggregate in particular biological pathways and that these pathways are frequently shared between disorders.” The consortium published its results in the Jan. 19, 2015, issue of Nature Neuroscience.

Orphan ALK’s mom found

Anaplastic lymphoma kinase, or ALK, is activated in a subset of lung cancers and glioblastomas, and is targeted by therapies such as Xalkori (crizotinib, Pfizer Inc.). Now, researchers from Yale University have identified its ligand in the body. ALK had been one of the few remaining kinases whose natural activator was unclear. In their research, the team showed that some forms of heparin bound to ALK. Heparin comes in several lengths, and the authors found that while short heparin chains did not activate ALK upon binding, longer heparin chains did. The team concluded that “heparin and perhaps related [molecules] function as ligands for ALK, revealing a potential mechanism for the regulation of ALK activity in vivo and suggesting an approach for developing ALK-targeted therapies for cancer.” They published their work in the Jan. 20, 2015, issue of Science Signaling.

Continues on next page
**AAV and HCC**

A team from the Human Genome Research Institute has gained new insights into the factors determining whether the use of adeno-associated virus (AAV) as a gene therapy vector can spell trouble for the liver. AAV is being used in several clinical gene therapy studies. One preclinical study has found that treatment with AAV could lead to liver cancer, but other studies have seen no liver toxicity issues, and so the authors wanted to look at the purported link between AAV and liver problems in more detail. Using a large cohort of mice treated with AAV-delivered gene therapy for a metabolic disorder, they found that integration of the viral vector into a specific site could indeed lead to liver cancer in mice, but that the risk could be influenced by the vector dose and timing of administration, as well as by the choice of enhancers and promoters. “Together, our results define aspects of AAV-mediated gene therapy that influence genotoxicity and suggest that these features should be considered for design of both safer AAV vectors and gene therapy studies.” They published their work in the Jan. 20, 2014, issue of the *Journal of Clinical Investigation*.

**Antibody-hormone fusion has staying power**

Scientists from the Scripps Research Institute have managed to produce fusion proteins consisting of the antibody Herceptin (trastuzumab) and different hormones, leading to therapeutics that were more stable, and so more active, than the hormones by themselves. Hormones and antibodies are at opposite ends of the longevity spectrum – while antibodies can last weeks or months, hormones, including the therapeutic variety, are degraded within a matter of hours and so need to be administered frequently, which reduces compliance. In their work, the authors fused either recombinant leptin or recombinant human growth hormone to Herceptin. They showed that the resulting fusion proteins were produced by yeast with good yield and had long-half lives and biological activity in rodent studies. The team based their linker on the structure of a bovine antibody and said it believed its approach “likely provides a general, relatively straightforward platform for generating antibody agonists and antagonists for a range of therapeutic applications.” The researchers described their work in the Jan. 19, 2015, issue of the *Proceedings of the National Academy of Sciences*.

**Proteomic atlas published**

A multinational team led by scientists from the Swedish Royal Institute of Technology has published an atlas of which human proteins are found in each of 32 different tissues. Using RNA expression data and immunohistochemistry, the authors investigated five different sets of proteins in those 32 tissues, namely the human secretome, the membrane proteome, the druggable proteome, the cancer proteome and metabolic proteins. Their methods allowed them to see which proteins were expressed where, down to the single cell level. The full data were also deposited in a public database, and the authors reported summary data in the Jan. 22, 2015, issue of *Science*.

**Bacteriophages in disease . . .**

Studies on the gut microbiome, whether in health or disease, have focused, in large part, on bacteria. Now, researchers from Washington University in St Louis have demonstrated that the viral composition of the gut microbiome, too, is altered in Crohn’s disease and inflammatory bowel disease. In their work, the authors looked at the enteric virome, the sum total of viral species found in the human gut. They discovered that patients with Crohn’s disease or ulcerative colitis had, on the average, a less diverse group of viruses in their gut than healthy individuals. Importantly, the changes in viral diversity – which included changes in bacteriophages, viruses that infect bacteria – appeared to be a consequence rather than a cause of the decreased bacterial diversity that is also present in Crohn’s disease and ulcerative colitis. The authors concluded that “the virome is a candidate for contributing to, or being a biomarker for, human inflammatory bowel disease and speculate that the enteric virome may play a role in other diseases.” Their findings appeared in the Jan. 22, 2105, issue of *Cell*.

. . . and as treatment

Bacteriophages are also an experimental cancer therapy, and researchers from Ohio State University have shown that the T-cell response that is induced by oncolytic viruses may be as important as their direct effects on tumors. The authors looked at three different types of tumors that differed in their susceptibility to treatment with bacteriophages, testing both how well viruses could fight the tumor cells in vitro and how much of a T-cell response they generated. “The in vitro permissiveness to viral oncolysis was not predictive of the in vivo antitumor effect, as all three tumors showed intact interferon signaling and minimal permissiveness to virus in vivo. Tumor shrinkage was T-cell mediated with a tumor-interferon signaling and minimal permissiveness to viral oncolysis was not predictive of the in vivo antitumor effect, as all three tumors showed intact interferon signaling and minimal permissiveness to virus in vivo. Tumor shrinkage was T-cell mediated with a tumor-specific antigen response required for maximal antitumor activity,” the authors wrote. They concluded that “it is likely that a more complete understanding of the interplay between the immunologic immune microenvironment and virus infection will be necessary to fully leverage the antitumor effects of this therapeutic platform.” Their findings appeared in the Jan. 21, 2015, online edition of *Molecular Therapy – Oncolytics*.

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