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SERVING RETURNS

BY STEVE EDELSON, SENIOR EDITOR

China's Ally Bridge Group hit the investment world's radar in 2015 with its audacious move to take CRO WuXi PharmaTech Inc. private. If the firm and its partners can engineer the first fruits of that move with the listing of WuXi's biologics unit in Hong Kong this year, the question is what will be its next moves to generate outsized returns for its investors.

Ally Bridge, which has a about $1.5 billion under management across three funds and an international base of LPs, thinks its returns and continued visibility will come from a handful of public and private portfolio companies with transformative data events, the first of which should come this half.

The firm also says it is working on new private equity deals that will rival WuXi in terms of size and impact.

Ally Bridge is keeping its private equity plans under wraps, and does not disclose names of investments in its Asia hedge fund. But founder and CEO Frank Yu did share with BioCentury the portfolio companies the firm hopes will join the ranks of ear disorder company Otonomy Inc., a big win from 2015, and Tesaro Inc., the winner so far this year.

The task of maintaining its biotech returns could be challenging. Two of the firm's three public biotech investments in the first half already have at least doubled in price. In addition, Ally Bridge is hoping for a win in Alzheimer's disease, a space that is rife with failure, as well as the ability of several portfolio companies to differentiate themselves in the intensely crowded field of immuno-oncology.

"We had a nice hit with Otonomy and people said we were lucky. Then we did it again with Tesaro," said Yu. "People also said WuXi was a one-off big deal, but we're working on several of similar size and potentially higher profile. If these are just lucky hits, why do we keep getting them?"

Because of the variety of investment types in its portfolio, Ally Bridge does not benchmark itself

"IF THESE ARE JUST LUCKY HITS, WHY DO WE KEEP GETTING THEM?"

FRANK YU, ALLY BRIDGE

against any single firm such as a KKR & Co. in the PE space or an OrbiMed Advisors LLC in public/private biotech investing.

"We don't want to copycat somebody else," said Yu. "We learn from the leaders and work with them and benefit from that, but we want to carve out our own niche. It's a good example of mixed martial arts — we've done venture capital, growth investments, cross-border deals and buyouts on a global basis. We're also mixed by being agnostic to product type, stage and geography."

BUILDING A BRIDGE

Yu, who founded Ally Bridge in 2013, had been a managing director at Goldman Sachs in Hong Kong. There, Yu got his first taste of cross-border dealmaking when he invested in China's LifeTech Scientific Corp. and then helped the device company partner with Medtronic Inc. (now Medtronic plc) in 2012.

Medtronic bought a 19% upfront stake and gained distribution rights to LifeTech's devices for structural heart defects, vascular disease and heart valve disease.

Yu said LifeTech was overlooked by other investors because the heart valve market in China was almost non-existent.

"Elsewhere, however, this is a billion dollar market. Our due diligence on a global market helped the company with local deal-making," said Yu. "With LifeTech I got a hidden gem and got a 7-10x return. Without that spark, there would be no Ally Bridge."

UNLOCKING WUXI

Yu concluded the name of the game was cross-border investing and M&A. Thus, job one after founding Ally Bridge was building a network in the U.S. The firm invested in at least 13 private U.S. companies from November 2013 to December 2015.

"We did medtech in Minneapolis, covered the life science hubs in California and did three companies in Boston," said Yu. The average number of investors in a syndicate was five, including such names as OrbiMed, New Enterprise Associates (NEA), Arch Venture Partners and RA Capital.

In early 2015, Yu came to a contrarian conclusion that would end up altering the course of Ally Bridge — the valuation of NYSE-listed WuXi was far lower than he thought it should be.

At the time, the CRO's market cap was nearly $3 billion.

"I became convinced of a unique investment thesis for WuXi when most other people thought it was expensive," said Yu. "A lot of the biggest investment funds knew WuXi was a good company but they didn't understand what it could mean to China's drug development industry."

At the time, Yu said, about 10% of WuXi's revenues came from China. He thought the figure was going to surge, thanks largely to moves by the Chinese government to encourage innovation and nation-wide recognition that innovation was essential to the country's future.

The expectation of much more business for WuXi in China coincided with a bubble in the country's equity markets that saw valuations far outstrip those of U.S. comparators. As a result, Yu reasoned that listing WuXi in China would benefit from significant arbitrage as well as scarcity value from being what he called one of the few world-class companies in China.

On April 30, 2015, a syndicate led by Ally Bridge and WuXi Chairman and CEO Ge Li announced plans to take the company private for $46 per ADS, or $3.3 billion. The price was a 16% premium to WuXi's close of $39.50 on April 29.

This year, the syndicate hopes to see the first payday when the private holding company that emerged, dubbed New WuXi Life Science Ltd., lists its biologics unit on the Hong Kong Stock Exchange. The IPO could value the unit at $1.5-$2 billion.

"This is a big chicken that will hatch a couple of eggs," said Yu. Other candidates could be New WuXi's main operating unit, which is called WuXi AppTec, and WuXi Genome Center, which provides sequencing services.

New WuXi has not described specific plans for those units, but Yu said the syndicate expects the sum of the parts will be worth much more than $3.3 billion.

"The minimum sum should be 2-3x the take-private value," he said.

ALLY'S ENCORE

Ally Bridge's post-WuXi moves have not yet rivaled the PE transaction in terms of audacity, but Yu noted returns trump headlines and said the firm is neither hurting for deal flow nor for additional potential home runs in its portfolio.

The strongest returns this year include a 3x paper gain on Tesaro, and a locked-in 2x on surgical robot company Medtech S.A.

The firm participated in Tesaro's February private placement of $155 million through the sale of 4.4 million shares at $35.19.

In late June, Tesaro jumped $40.19 (108%) to $77.40 after its niraparib met the primary endpoint of improving progression-free survival (PFS) in the Phase III NOVA trial as maintenance therapy in platinum-sensitive ovarian cancer patients with and without germline BRCA mutations.

Tesaro hasn't looked back and closed Friday at $96.35. Ally Bridge owns less than 1% of the biotech.

The firm invested in Medtech in December when it purchased $15 million of convertible bonds and warrants. In July, Zimmer Biomet Holdings Inc. bought the French company for €50 per share ($55.26), or about $132 million.

Ally Bridge paid €30.10 for each bond and warrant, and Zimmer bought the firm's stake for €67.20 per bond and warrant.

"The Medtech deal was an upset to European and U.S. investors," said Yu. "Leading funds in France are saying 'how did we miss it?' Big name Wall Street healthcare funds also were approached, but didn't want to bother with something from France. We did a lot of homework that others didn't bother to do. We talked to neurosurgeons at the Cleveland Clinic who were using the product and didn't even know it was from a French company."

Medtech's robot essentially functions as a physician assistant during brain surgeries and assists in a variety of open skull procedures.

BETTING ON BIG MARKETS

The next batch of Ally Bridge's newsmakers contains a mix of established mechanisms for large market diseases such as diabetes, AD and osteoarthritis.

ALLY BRIDGE'S PORTFOLIO

Ally Bridge Group has disclosed investments in at least 17 biotech companies, several of which are developing potentially first-in-class or best-in-class technologies. Details on the size of the firm's investments were not disclosed. Portfolio companies grouped below based on indication of lead program. *Source: Ally Bridge, BCIQ: BioCentury Online Intelligence.*

Company	Lead program	Phase
Cancer		
Tesaro Inc. (NASDAQ:TSRO)	Varubi rolapitant, a neurokinin 1 (NK1) substance P receptor (TACR1) antagonist to treat chemotherapy-induced nausea and vomiting	Mkt
Cold Genesys Inc.	CG0070, a modified adenovirus expressing granulocyte macrophage colony-stimulating factor (GM-CSF; CSF2) to treat bladder cancer	Ph III
Sorrento Therapeutics Inc. (NASDAQ:SRNE)	Four biosimilar mAbs for cancer and autoimmune indications licensed from **Mabtech Ltd.**	Ph III
Adaptimmune Therapeutics plc (NASDAQ:ADAP)	ADAP NY-ESO TCR, an enhanced T-cell therapy targeting cancer/testis antigen 1B (NY-ESO-1; CTAG1B) to treat cancer	Ph I/II
3-V Biosciences Inc.	TVB-2640, a first-in-class fatty acid synthase (FASN; FAS) inhibitor to treat solid tumors	Ph I
Aeglea BioTherapeutics Inc. (NASDAQ:AGLE)	AEB1102, a first-in-class a pegylated human recombinant arginase 1 (ARG1) to treat cancer	Ph I
Apexigen Inc.	APX005M, agonistic humanized mAb that targets CD40 to treat solid tumors	Ph I
Cellectis S.A. (Euronext:ALCLS; NASDAQ:CLLS)	UCART19, chimeric antigen receptor (CAR)-modified, CD19-targeted allogeneic T cells to treat CD19-positive B cell acute lymphoblastic leukemia	Ph I
ImmunGene Inc.	IGN002, interferon (IFN) alpha linked to an anti-CD20 mAb to treat CD20-positive cancers	Preclin
Other indications		
AltheaDx Inc.	IDgenetix, a test to detect alterations in cytochrome P450 genes that predicts metabolism of drugs for cardiovascular, neurological and thrombotic indications	Mkt
Otonomy Inc. (NASDAQ:OTIC)	Otiprio ciprofloxacin otic suspension to treat otitis media	Mkt
Hua Medicine Ltd.	Sinogliatin, a small molecule glucokinase (GCK; GK) activator to treat Type II diabetes	Ph II
Alzheon Inc.	ALZ-801, an oral small molecule prodrug of tramiprosate to treat Alzheimer's disease	Ph I
Kato Pharmaceuticals Inc.	Resolvine, an intravitreal injection to treat vitreomacular attachment	Ph I
Pieris Pharmaceuticals Inc. (NASDAQ:PIRS)	PRS-080, a first-in-class anticalin hepcidin antagonist to treat anemia	Ph I
Symic Biomedical Inc.	First-in-class artificial proteoglycan mimetics: SB-030 mimics decorin to treat cardiovascular diseases and SB-061 mimics aggrecan to treat osteoarthritis	Ph I
Tunitas Therapeutics Inc.	Epsi-gam, a first-in-class fusion protein comprising the Fc portions of human IgE and IgG1 to treat asthma	Ph I

Yu said Alzheon Inc. and Hua Medicine Ltd. are among the portfolio's private companies with significant upside.

The firm led Alzheon's $17 million series A round last year. In 1H17, the company's ALZ-801 is expected to start Phase III testing to treat mild to moderate Alzheimer's patients homozygous for apolipoprotein E epsilon 4 (APOE4).

ALZ-801 is an oral small molecule prodrug of tramiprosate. The parent molecule failed to show efficacy in the total AD population in a pair of Phase III trials run by Bellus Health Inc. But Alzheon is pursuing the APOE4 subgroup, which comprises 10-15% of the AD population, based on an analysis of the Phase III studies that showed significant improvements in cognition at multiple time points for homozygous patients.

"WE'VE ALWAYS BELIEVED WE SHOULD BE WORTH MORE THAN $1 BILLION."

HENRY JI, SORRENTO

Alzheon has not provided a timeline for when it expects data for ALZ-801.

"Alzheon could be a huge home run," said Yu. "Alzheimer's is a high-risk indication but also has some of the highest returns."

The biotech is raising more money but has not disclosed details.

Hua Medicine has perhaps the nearest data milestone of Ally Bridge's companies. This year, the company expects results from a Chinese Phase II trial of HMS5552 to treat Type II diabetes.

Hua in-licensed the small molecule glucokinase (GCK; GK) activator from Roche in 2012. Three years later, Ally Bridge led company's $25 million series B round, and also participated in this year's $50 million series C.

"This is definitely one of the highest potential companies to be a home run," said Yu. "The China Type II diabetes market is 200 million patients and growing."

Last year, Hua reported Phase Ic data from an open-label trial in which once- and twice-daily 75 mg HMS5552 reduced mean HbA1c by 1% at week four from a baseline HbA1c of 8.9%.

Hua said HMS5552's effects were more rapid than many other diabetes therapies. The company also said the fourth-generation compound's amino acid-based scaffold should have a better safety profile than prior GCK activators that used tri-benzenoid scaffolds and caused hypoglycemia and elevated triglycerides.

While Ally Bridge's bets in AD and diabetes focus on single assets, portfolio company Symic Biomedical Inc. has at least five products in development for about 13 diseases. The biotech is developing therapeutics that mimic proteoglycans, which are macromolecules found in the extracellular matrix.

Symic's clinical-stage assets are SB-030, a mimic of Decorin, and SB-061, a mimic of aggrecan.

This half, the biotech plans to update its enrollment progress in the Phase I/II SHIELD study of SB-030 to reduce neointimal hyperplasia following percutaneous transluminal angioplasty (PTA).

Next May, the company expects to have results from a Phase I/II trial of SB-061 to treat mild to moderate osteoarthritis of the knee. The product is partnered with Nordic Bioscience A/S.

CUTTING EDGE IN CANCER

The common thread among Ally Bridge's oncology portfolio is a desire to own first or best-in-class approaches.

"We need to be in as many cutting edge technologies as we can be," said Yu. "Nobody else coming out of Hong Kong is doing cutting edge investing in the U.S."

For example, Ally Bridge's investment in Tesaro hinged on the biotech's potentially best-in-class PARP inhibitor. First-in-class examples include oncolytic viruses from Cold Genesys Inc., T cell receptor (TCR) therapies from Adaptimmune Therapeutics plc, and multiple programs from Sorrento Therapeutics Inc. such as natural killer cell-based products and cell-penetrating antibodies.

With Sorrento, Yu said, the goal is to best the returns from Tesaro. "Sorrento is definitely a higher beta stock, so with that higher beta we're looking for a higher return," he said.

Ally Bridge led a $150 million private placement for Sorrento that closed in early June. The biotech sold stock at $5.55 and issued warrants to buy additional shares at $8.50. Sorrento closed Friday at $6.52, up 17% from the private placement with a market cap of $427 million.

"We've always believed we should be worth more than $1 billion," said President and CEO Henry Ji.

He plans to reach that valuation through a series of partnerships for chimeric antigen receptor (CAR) tumor-attacking NK cells and internal development of cell-internalizing antibodies.

"Nobody has been able to conquer intracellular antibody delivery," said Yu. "That program itself could have huge upside. And Sorrento is a leader in NK cells, which have been overlooked by the investment community."

NK cells have the ability to non-specifically find and destroy tumor cells and other abnormal cells. In addition, their mechanism avoids some of the key liabilities of T cell therapies.

Sorrento has a deal with NantKwest Inc. to develop next-generation CAR.TNK immunotherapies.

Ally Bridge's other immuno-oncology investments also are looking to differentiate themselves from the leading autologous CAR T companies. For example, Cellectis S.A. is creating an off-the-shelf approach using universal donor CAR T cells.

The company's UCART19 is in Phase I testing to treat pediatric patients with relapsed or refractory CD19-positive B cell acute lymphoblastic leukemia (ALL). The product consists of CAR-modified CD19-targeted allogeneic T cells.

Cellectis' partner, Servier, has not disclosed a timeline for when it expects data.

Adaptimmune is developing TCR therapeutics, which could address a broader range of cancer targets than CARs. TCRs recognize processed antigenic peptides presented by major histocompatibility complex (MHC) class I molecules on the surface of a cell. The targets thus can be antigens derived from intracellular or extracellular proteins as long as they are processed and displayed as MHC complexes. In contrast, CAR targets are extracellular.

Adaptimmune and partner GlaxoSmithKline plc were planning to start pivotal testing of ADAP NY-ESO TCR to treat synovial sarcoma this year. Last week, however, FDA placed a partial clinical hold on the planned trial and asked for CMC and trial design information. Adaptimmune plans to submit its response shortly.

The product consists of autologous T cells genetically modified to express TCRs targeting cancer/testis antigen 1B (NY-ESO-1; CTAG1B).

The product has Orphan Drug and breakthrough therapy designations from FDA.

Cold Genesys has one of the latest-stage oncolytic viruses in the industry, although it does not have a near-term milestone. The company's CG0070 is in Phase III testing to treat bladder cancer, with data expected in 2019. The product is a modified adenovirus encoding GM-CSF.

In the interim, the company plans to advance an internal checkpoint modulator into clinical trials and to test combinations of its two lead assets.

"Oncolytics are going to be an inevitable component of immune stimulation," said Yu.

WUXI BACKSTOP

While Sorrento and Tesaro represent Ally Bridge's push to expand its investments in publicly traded biotechs, the firm expects to continue seeking novel private opportunities.

The said it is able to make investments in cutting edge, unproven technologies because it views WuXi as such a low-risk investment.

"WuXi has a long tail and a defendable, low-risk service business. It's very different from speculating on clinical data," said Yu. "They're really the backbone of the whole portfolio."

As to the next big PE, play, Yu is keeping the cards close to his chest. "WuXi is just the beginning — we're working on several deals of similar size that are potentially higher profile," he said. bc

COMPANIES AND INSTITUTIONS MENTIONED

Adaptimmune Therapeutics plc (NASDAQ:ADAP), Abingdon, U.K.
Ally Bridge Group, Hong Kong, China
Alzheon Inc., Framingham, Mass.
Bellus Health Inc. (TSX:BLU), Laval, Quebec
Cellectis S.A. (Euronext:ALCLS; NASDAQ:CLLS), Paris, France
Cleveland Clinic, Cleveland, Ohio
Cold Genesys Inc., Santa Ana, Calif.
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
Hua Medicine Ltd., Shanghai, China
LifeTech Scientific Corp. (HK:1302), Shenzhen, China
Medtech S.A. (Euronext:ROSA), Montpellier, France
Medtronic plc (NYSE:MDT), Dublin, Ireland
NantKwest Inc. (NASDAQ:NK), Cardiff-by-the-Sea, Calif.
New WuXi Life Science Ltd., Shanghai, China
Nordic Bioscience A/S, Herlev, Denmark
Otonomy Inc. (NASDAQ:OTIC), San Diego, Calif.
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
Servier, Neuilly-sur-Seine, France
Sorrento Therapeutics Inc. (NASDAQ:SRNE), San Diego, Calif.
Symic Biomedical Inc., Emeryville, Calif.
Tesaro Inc. (NASDAQ:TSRO), Waltham, Mass.
U.S. Food and Drug Administration (FDA), Silver Spring, Md.
Zimmer Biomet Holdings Inc. (NYSE:ZBH), Warsaw, Ind.

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Osherovich, L. "Once more, with APOE4." *BioCentury* (2013)

PRODUCT DEVELOPMENT

NO ANTIGEN LEFT BEHIND

BY EMILY CUKIER-MEISNER, SENIOR WRITER

Amgen Inc. partnered with Advaxis Inc. to develop a personalized neoantigen therapy platform with potential to invoke a broad immune response by both stimulating the immune system on multiple fronts and delivering the full repertoire of a patient's potential neoepitopes.

Advaxis' ADXS-NEO uses a live attenuated form of *Listeria monocytogenes* bacteria to deliver a complete roster of patient-specific neoantigens directly to immune cells.

Under the Aug. 2 deal, Amgen will receive exclusive, worldwide rights to develop and commercialize ADXS-NEO in exchange for $40 million up front and a $25 million equity investment. Advaxis, which also is eligible for $475 million in milestones, plus royalties, will lead development through Phase II clinical proof of concept (POC) and be responsible for manufacturing the therapy.

The deal is at least the third neoantigen collaboration to be announced this summer. In May, Gritstone Oncology Inc. partnered to deliver its personalized neoantigen vaccines using Immune Design Corp.'s Zvex viral delivery technology. Terms are undisclosed.

In June, Merck & Co. Inc. agreed to pay Moderna Therapeutics Inc. $200 million up front to develop mRNA-based personalized neoantigen vaccines through clinical POC. The partners planned to combine the vaccines with immunotherapies, including the pharma's PD-1 inhibitor Keytruda pembrolizumab.

The deals came on the heels of publications suggesting that neoantigen-specific T cells are the primary mediators of the immune response unleashed by checkpoint inhibitors and could be the key to increasing response rates to them.

Amgen's oncology pipeline lacks an anti-PD-1 or anti-PD-L1 agent. It does include AMG 228, an immunotherapeutic mAb targeting glucocorticoid-induced tumor necrosis factor receptor (TNFR)-related protein (GITR; TNFRSF18) that is in Phase I testing to treat solid tumors.

SVP of BD David Piacquad said the deal is part of Amgen's focus on acquiring immuno-oncology technology. The company's arsenal already includes bispecific technologies from the 2012 acquisition of Micromet Inc. and a 2015 partnership with Xencor Inc., chimeric antigen receptor (CAR) T cell therapies from a 2015 collaboration with Kite Pharma Inc., and an oncolytic virus platform from the 2011 acquisition of BioVex Inc.

Last year the latter yielded the first oncolytic virus therapy approved in the U.S., Imlygic talimogene laherparepvec (T-Vec).

"With Imlygic, the first approved oncolytic vaccine, we feel we've developed significant insights into the oncology vaccines field," said Piacquad in an email to BioCentury.

SVP of Global Development Elliott Levy added that Amgen was looking for immunotherapy technologies with the potential to stimulate a tumor-specific T cell response, activate innate immunity and modify the tumor microenvironment.

"We were attracted to Advaxis' platform because it accomplishes each of the three mechanistic goals," he said.

Levy said the ability to deliver a large number of neoantigens was also important.

"What was unique about Advaxis' approach is it doesn't rely on any prior assumptions about which tumor-specific antigens are the drivers of an immune response," he said.

> "WE CAN PRESENT LITERALLY EVERY POSSIBLE NEOEPITOPE THAT THE IMMUNE SYSTEM MIGHT RESPOND TO."
>
> ROBERT PETIT, ADVAXIS

Amgen's previous work with Imlygic was one reason Advaxis chose the big biotech as a partner.

"The thing we like most is they totally understood what we are doing: the value of using a whole attenuated live organism, and how much that can mean to the breadth and character of the immunologic response," said Advaxis EVP and CSO Robert Petit.

The initial focus will be on solid tumors because of greater unmet need. Petit said the partners have not yet decided what indications or combinations they may pursue, but will do so via a joint development committee to include equal representation from Advaxis and Amgen.

The partners plan to begin clinical testing next year.

FULL COVERAGE

Advaxis' platform co-opts the immune system's response to *Listeria* infection to also attack antigens of interest that the company engineers into the bacterium.

In the setting of infection, *Listeria* in the bloodstream is rapidly engulfed by immune cells such as antigen presenting cells, which translocate the bacterium to the lysosome to be digested. Listeria then releases listeriolysin O (LLO), a pore-forming toxin, to escape the lysosome and enter the cytoplasm. The pathogen is cleared when the proteins it expresses in cytoplasm are presented to the immune system by major

ANTIGEN-BEARING BACTERIA

The personalized neoantigen vaccine platform developed by **Advaxis Inc.** (NASDAQ:ADXS) uses *Listeria monocytogenes* to provoke both a broad and specific antitumor immune response.

(1) Advaxis begins by sequencing a patient's cancerous and normal cell DNA to identify cancer-associated mutations known as neoantigens. Attenuated *Listeria* are transformed by DNA plasmids encoding antigens of interest (shown in blue, yellow and purple) and a truncated listeriolysin O (tLLO) (shown in orange) to form ADXS-NEO (shown in green).

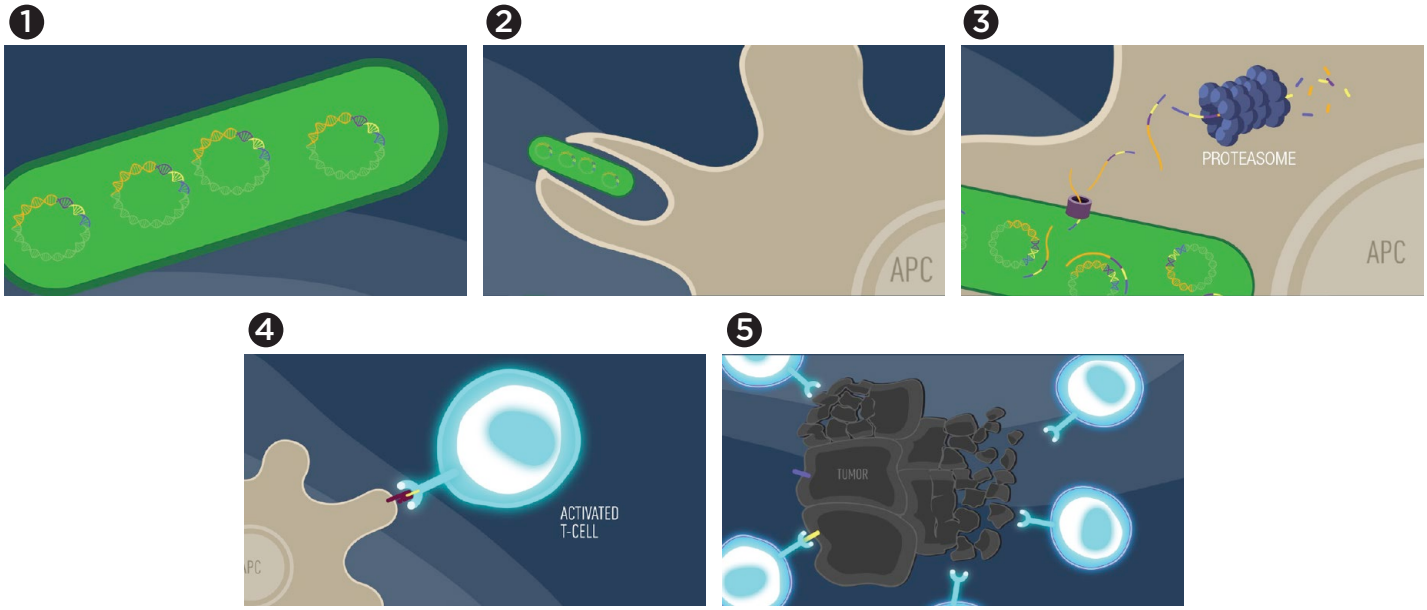
(2) ADXS-NEO is phagocytosed by immune cells including antigen-presenting cells (APCs).

(3) The encoded tLLO and neoantigens are expressed in the cytosol of the APC where they are processed by proteasomes into small (~9 amino acid) peptides.

(4) Neoepitope peptides form complexes with major histocompatibility complex (MHC) class I receptors and are presented on the surface of APCs to T cells, resulting in T cell activation.

(5) Activated T cells mediate a cell-based immune response to seek out and destroy tumors bearing the neoepitopes. tLLO reduces the activity of immunosuppressive factors like Tregs and myeloid-derived suppressor cells in the tumor microenvironment.

Source: Advaxis



histocompatibility complex (MHC) class I molecules, which trigger a cellular immunity response.

Advaxis uses an attenuated form of *Listeria* that cannot be transmitted from cell to cell, which eliminates its virulence but still can express proteins to evoke an immune response. The company transduces the bacteria with a DNA vector that encodes the desired tumor antigen or antigens and a truncated form of LLO as an adjuvant (see "Antigen-Bearing Bacteria").

Petit said in addition to delivering antigens to the cells responsible for training the immune system, using *Listeria* also puts the body in a highly immunogenic state.

"When a billion bacteria show up in your blood stream, that's a crisis to the immune system: all the alarms go off and all the attention is focused on this response," he said.

Petit said invoking cellular immunity is the most effective way of targeting cells for destruction.

"It requires cellular immunity to clear the infection, and that same cellular immunity is required to eliminate cells that have gone bad and have cancer," he said.

To make patient-specific neoantigen vaccines, Petit said Advaxis had to scale down its manufacturing process to make single-patient batches and optimize the DNA plasmid for insertion of a patient-specific DNA sequence. He declined to provide details on the challenges and how the company solved them.

He said Advaxis is still optimizing the software needed to design the DNA vectors that encode the neoantigens, but once that is accomplished the company can rely on its established methods for manufacturing the plasmids, transducing and growing the *Listeria*.

Petit said the platform could invoke a broader immune response than other neoantigen delivery mechanisms because it preserves the multi-component immune response triggered by *Listeria* infection. This includes alterations in the immunologic macroenvironment by engaging

pathways evoked by toll-like receptors (TLRs), pathogen-associated molecular patterns, caspase recruitment domain family member 4 (NOD1; CARD4) and NOD2 (CARD15), and transmembrane protein 173 (STING; TMEM173).

He added the truncated LLO helps suppress the activity of Tregs and myeloid-derived suppressor cells (MDSCs) in the tumor microenvironment.

Petit said it remains to be seen whether the immune response resulting from using *Listeria* as a vector could be sufficiently effective as monotherapy. At the March 2015 American Association for Cancer Research meeting, Advaxis presented animal data showing enhanced antitumor activity when axalimogene filolisbac (ADXS11-001) was combined with either an anti-PD-1, anti-OX40 (tumor necrosis factor (TNF) receptor super family member 4; TNFRSF4; CD134) or anti-GITR mAb.

Axalimogene filolisbac is a live *Listeria monocytogenes*-based immunotherapy expressing E7 transforming protein (human papillomavirus-16; HpV16gp2) that has completed Phase II testing to treat cervical cancer.

Another distinguishing feature of Advaxis' technology is that it forgoes neoantigen selection in favor of the brute force method: delivering them all.

Advaxis identifies candidate neoantigens by sequencing and comparing a patient's cancerous biopsies to normal cells. But rather than using either public or proprietary algorithms to winnow down the number of neoepitopes — a given patient can have over a thousand — Petit said it's feasible to deliver all the antigens at once using the Advaxis platform.

In a March investor presentation, the company said each bacterial construct can encode 25-50 neoepitopes for delivery to T cells. Petit said Advaxis plans to make multiple constructs to cover a patient's neoantigen spectrum.

Because Listeria spends most of its time within cells, Petit said it is unlikely to promote neutralizing antibody formation. Advaxis thus thinks the approach can be used multiple times in the same patient as needed, using the same neoantigens or a different set identified after a patient's cancer changes over time.

While the predictive power of competitors' algorithms remains to be seen, Petit said, including all the antigens might increase the proportion of patients who respond to the Advaxis vaccine.

"We can present literally every possible neoepitope that the immune system might respond to, and the immune system will respond as it will. But we don't run the risk of eliminating potentially useful ones by trying to predict them with some algorithm," he said.

Advaxis said it can produce a personalized neoantigen vaccine in about six weeks. Moderna has said it can do so in "weeks." bc

COMPANIES AND INSTITUTIONS MENTIONED

Advaxis Inc. (NASDAQ:ADXS), Princeton, N.J.
American Association for Cancer Research (AACR), Philadelphia, Pa.
Amgen Inc. (NASDAQ:AMGN), Thousand Oaks, Calif.
Gritstone Oncology Inc., Emeryville, Calif.
Immune Design Corp. (NASDAQ:IMDZ), Seattle, Wash.
Kite Pharma Inc. (NASDAQ:KITE), Los Angeles, Calif.
Merck & Co. Inc. (NYSE:MRK), Kenilworth, N.J.
Moderna Therapeutics Inc., Cambridge, Mass.
Xencor Inc. (NASDAQ:XNCR), Monrovia, Calif.

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EMERGING COMPANY PROFILE

RESTRAINING TRANSLATION

BY VIRGINIA LI, STAFF WRITER

Bantam Pharmaceutical LLC is developing small molecule eukaryotic translation initiation factor 4E inhibitors that selectively inhibit translation of several tumor-promoting genes and disrupt cancer cell metabolism. It hopes to show the mechanism of its lead compound will lead to a therapeutic more potent or safer than competing compounds in the same pathway.

mRNA translation begins with binding of a ribosome to the 5' end of an mRNA. This is facilitated by eukaryotic initiation factors including the eukaryotic translation initiation factor 4F (eIF4F) complex, which comprises three subunits: eIF4E cap-binding protein, eIF4G scaffolding protein and eIF4A RNA helicase. According to Bantam CEO Michael Luther, eIF4E is the rate-limiting subunit of the eIF4F complex.

mRNAs with long 5' untranslated regions (UTRs) rely more heavily on eIF4E to initiate translation compared to mRNAs with short 5' UTRs.

Luther said the majority of mRNAs with long 5' UTRs code for oncogenes including cyclin D1 (CCND1; BCL1), VEGF, v-myc myelocytomatosis viral oncogene homolog (MYC; c-Myc) and ornithine decarboxylase (ODC). By contrast, mRNAs with short 5' UTRs code for normal housekeeping genes required to maintain basic cell functions.

eIF4E is overexpressed in many hematologic and solid cancers. Luther said inhibiting the target could disrupt formation of the eIF4F complex, leading to a selective decrease in translation of oncogenes without affecting translation of housekeeping genes.

Last year, Bantam acquired its eIF4E inhibitor program from Egenix Inc. for $5.1 million after Egenix filed for Chapter 11 bankruptcy. Bantam's founders are former Egenix shareholders.

Luther said Bantam has identified candidates more specific for eIF4E than Egenix's preclinical eIF4E inhibitor 4EGI-1. Bantam's compounds are negative allosteric modulators of eIF4E, although Luther said their precise molecular binding sites have not yet been established.

He added that unpublished *in vitro* data show Bantam's inhibitors disrupt cancer cell metabolism partly by altering their cellular redox status. The company is working to elucidate the mechanisms underlying its compounds' effects on metabolism.

BANTAM PHARMACEUTICAL LLC
New York, N.Y.

Technology: Small molecule inhibitors of eukaryotic translation initiation factor 4E

Disease focus: Cancer

Clinical status: Preclinical

Founded: 2015 by Lionel Goldfrank III, Victor Keen and W. James Tozer Jr.

University collaborators: McGill University, Hannover Medical School

Corporate partners: None

Number of employees: 3

Funds raised: $9 million

Investors: Lionel Goldfrank III, Victor Keen and W. James Tozer Jr.

CEO: Michael Luther

Patents: 3 issued covering composition of matter and indications for lead compound

Other unpublished *in vivo* data show Bantam's orally administered lead, BTM-1028, led to tumor regression in xenograft models of human B cell lymphoma and "nearly 100%" tumor growth inhibition in xenograft models of colorectal cancer. Luther said it has not led to any notable adverse events *in vivo*. Bantam plans to report the data by early next year. BTM-1028 is slated to enter the clinic in 2Q18 to treat B cell malignancies.

At least two other companies are targeting eIF4E. Onconova Therapeutics Inc.'s briciclib is a small molecule eIF4E inhibitor delivered via IV in Phase I to treat advanced solid tumors. The company is also developing a preclinical orally administered analog, ON 013100.

Translational Therapeutics Inc.'s ribavirin elaidate, a ribavirin derivative delivered using lipid vector technology, is expected to enter the clinic next year to treat thyroid cancer.

Compared to reported *in vitro* and *in vivo* data on briciclib and ON 013100, Luther said Bantam's lead has higher potency, which he believes stems from the combination of its effects on translation and cancer metabolism. "That's the whole nature of what we're sorting out right now, what gives us that increased potency," said Luther.

He added that Bantam's compound also has greater bioavailability than ON 013100.

Onconova spokesperson Benjamin Hoffman said the company is initially pursuing its IV formulation in proof-of-concept and safety studies. He declined to comment on ON 013100's bioavailability, but noted that briciclib and ON 013100 have demonstrated nanomolar potency against mantle cell lymphoma and gastric, esophageal and breast cancer cell lines.

Luther declined to compare Bantam's compound to ribavirin elaidate.

Another player in the space is Effector Therapeutics Inc., whose eFT508 targets a pathway upstream of eIF4E. Effector's compound inhibits MAP kinase interacting serine-threonine kinase 1 (MKNK1; MNK1) and MKNK2 (MNK2), which phosphorylate eIF4E and other tumor-promoting molecules. eFT508 is in a Phase I/II trial to treat advanced solid tumors.

Luther said Bantam's lead has a wider therapeutic index compared to data previously reported on eFT508.

Effector President and CEO Steve Worland said eFT508 is expected to have a wide therapeutic index because MNK1/MNK2 knockouts are fully viable, though noted "the true safety profile of a drug candidate can only be known from human studies." Data from its Phase I/II study of eFT508 are expected next year.

Luther said Bantam has enough funding to complete a Phase I study of BTM-1028. The company plans to seek a partner for further clinical development. bc

COMPANIES AND INSTITUTIONS MENTIONED

Bantam Pharmaceutical LLC, New York, N.Y.
Effector Therapeutics Inc., San Diego, Calif.
Onconova Therapeutics Inc. (NASDAQ:ONTX), Newton, Pa.
Translational Therapeutics Inc., Arlington, Mass.

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REGULATION

ADAPTING FOR THE REAL WORLD

BY STEPHEN HANSEN, ASSOCIATE EDITOR

Two years after launching a pilot program for its adaptive pathways initiative, EMA says work remains to develop better strategies for using real-world evidence to validate conditional approvals and to increase patient and payer involvement. The initiative could benefit from two Innovative Medicines Initiative projects that seek to develop methods and tools for collecting and interpreting real-world data, particularly in an adaptive licensing setting.

EMA launched the adaptive pathways program in 2014 to allow companies to market new products for limited populations based on promising but early data, followed by iterative approvals for additional populations based on postmarket trials and real-world data.

The pilot project, which has concluded, advanced six candidate drug programs into parallel EMA-health technology assessment (HTA) scientific advice and one into traditional scientific advice.

EMA's Francesca Cerreta told BioCentury the agency launched the pilot because payers and HTA bodies believed they didn't have sufficient data to evaluate products with conditional approval.

The process begins by bringing together the stakeholders to discuss a development plan for a drug candidate that would allow data to be generated to meet the needs of regulators, HTA bodies and payers, as well as patients.

According to Cerreta, a scientific officer in EMA's Product Development Scientific Support Department, the aim of adaptive pathways is to take an early look at a development plan and optimize it "so that we can address the needs of several decision makers at an early stage, and build those requirements into the development plan." The intended result is a regulatory pathway that balances timely patient access and the need for sufficient information on the benefits and risks.

The pathway is intended for programs in Phase I or Phase II that have shown early signs of efficacy. Companies may seek initial marketing authorization for a subgroup or limited population with the highest unmet need by demonstrating a positive benefit-risk profile in smaller/faster clinical trials.

Following initial approval, the product's label could be expanded — or narrowed — as evidence is gathered from additional clinical trials and real-world experience in other patient populations.

Sixty-two proposals were submitted during the two-year pilot. Twenty were accepted for initial discussions, with seven advancing. Indications spanned gastrointestinal, cardiovascular, anti-infectives and neurology, with cancer the largest at 33% of submissions.

In its final report on the pilot published on Aug. 3, EMA said a primary challenge faced by sponsors was identifying "methodologically sound strategies of real-world evidence collection to support the assessment of efficacy and effectiveness."

> "COMPANIES NEED TO ASK THE FUNDAMENTAL QUESTION, WHICH IS WHAT PURPOSE DO THE REAL-WORLD DATA SERVE?"
>
> FRANCESCA CERRETA, EMA

According to Cerreta, the lack of a strategy to collect real-world evidence was one of the main reasons most of the programs didn't advance beyond initial discussions.

Germany's HTA body, the Institute for Quality and Efficiency in Health Care (IQWiG), was quick to criticize the initiative in the wake of the report, citing EMA's findings as confirmation of the limitations of using real-world evidence to draw conclusions about the efficacy or safety of a drug after it is approved.

IQWiG also charged EMA made no proposals of its own on how real-world data could be used for a drug approval.

Cerreta did not agree, telling BioCentury that EMA's report highlighted examples of real-world data already considered acceptable by EMA, such as postmarket registries, single-arm trials with comparator data collected from registries, and efficacy and safety data from compassionate use programs.

Instead, she said, the report highlighted how most companies didn't have a clear vision of how they plan to incorporate real-world data into the development plan for generating supplementary safety or efficacy data for their compounds.

For example, EMA rejected some proposals because the real-world evidence component simply stated the company would launch a registry, if required. "It wasn't particularly innovative, so it didn't really provide reassurance that the company really had an understanding of how to build-in or pre-plan the data collection," Cerreta said.

"Companies need to ask the fundamental question, which is what purpose do the real-world data serve?" she said.

If sponsors have a clear plan for how the real-world data will be used, then stakeholders in the adaptive pathways process can discuss the best ways to collect the data and whether it is feasible, she added.

Cerreta said methodologies to correlate hard clinical endpoints with "real-world endpoints," such as time to treatment failure and survival, are still in the early stages of development. Until these new methodologies are validated, companies should select endpoints for real-world data that

minimize the potential for bias, such as overall survival or virologic load, she said.

"At this stage we are more prepared to accept real-world data endpoints that are really clear cut," Cerreta said.

Cerreta and Pär Tellner of the European Federation of Pharmaceutical Industries and Associations (EFPIA) both pointed to two IMI projects — ADAPT SMART and GetReal — that could provide the tools and methodologies companies and regulators need to routinely collect and interpret real-world evidence. Tellner is director of regulatory affairs at EFPIA.

Launched in 2015, ADAPTSMART is an IMI consortium that is analyzing the opportunities and obstacles for adaptive licensing pathways. The group is reviewing tools and methods for real-world evidence generation, including methods to optimize non-conventional clinical trials and to link patient-relevant outcomes in the real-world to clinical endpoints.

GetReal is a consortium launched in 2014 to develop new methods for real-world evidence collection and synthesis.

The project seeks to develop and validate tools to design trials that use real-world evidence, as well as decision-making tools for companies to use real-world evidence in the premarket setting and for regulators and payers to weigh the benefit-risk and value of a therapy.

EMA is a partner in both IMI projects.

Cerreta noted a third project also may help: EMA's initiative to develop standards for the design and operation of registries, which was launched in 2014.

EMA hasn't published guidance that directly addresses the collection of real-world evidence, but Cerreta noted that guidance on methods for collecting such data already exist as part of the agency's guidelines on good pharmacovigilance practices for post-authorization safety studies, and in methodological standards in pharmacoepidemiology published by the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP).

Last month, FDA's Center for Devices and Radiological Health (CDRH) published draft guidance on the use of real-world evidence in regulatory decision-making for devices, while FDA's Center for Drug Evaluation and Research (CDER) is committed under PDUFA VI to publish similar draft guidance for drugs by 2021.

PATIENTS AND PAYERS

Beyond the matter of real-world evidence, EMA's final report said increased patient and payer involvement would improve the adaptive pathways process.

Cerreta said patient participation can be particularly valuable to assessing the relevance of endpoints. She cited a case in which a participating patient flagged an endpoint chosen by a company as not feasible because clinical practice varied too greatly across individual European countries.

Cerreta said patients also have provided input on the development of patient-reported outcomes (PROs).

"These are issues where patients can have a very valuable knowledge," she said.

According to Cerreta, increasing patient involvement is mainly a logistical matter. In the adaptive pathways pilot, the short turnaround time from identifying a participating drug to the discussion phase made it difficult to get patients to the table.

In addition, because the pilot wasn't funded through industry fees, the agency did not have enough money to fly in patient representatives to participate.

If EMA moves forward with a formal adaptive pathways program, Cerreta said it would likely have more structured timelines and funding that would increase patient involvement.

On the payer side, Cerreta said some companies in the pilot wanted to explore adaptive pricing strategies linked to data collection; however, this was not possible because the relevant entities responsible for EMA member state decisions on pricing and reimbursement were not part of the pilot discussions.

EMA's report noted that future payer involvement would be important for addressing novel reimbursement strategies, such as annuity payment models or the design of registries where patient outcomes are tied to reimbursement.

Longer term questions on the utility of the adaptive pathways process — such as whether HTA bodies are willing to recommend new therapies based on limited data sets, and whether starting the data exclusivity clock earlier will lower a company's return on investment — won't be answered until a drug is approved using the adaptive licensing pathway.

The report said the adaptive pathways initiative, including programs accepted into the pilot, will be incorporated into the existing parallel regulatory-HTA scientific advice framework. Launched in 2010, parallel scientific advice speeds patient access by ensuring data generated by sponsors meets the needs of both regulators and HTA bodies, thus potentially avoiding delays in reimbursement decisions.

EMA plans to hold a workshop on Dec. 8 to discuss the adaptive pathways program. bc

COMPANIES AND INSTITUTIONS MENTIONED

European Federation of Pharmaceutical Industries and Associations (EFPIA), Brussels, Belgium

European Medicines Agency (EMA), London, U.K.

Institute for Quality and Efficiency in Health Care (IQWiG), Cologne, Germany

U.S. Food and Drug Administration (FDA), Silver Spring, Md.

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EBB & FLOW

LION'S SHARE OF THE WORK

Aslan Pharmaceuticals Pte. Ltd.'s 2011 deal with Bristol-Myers Squibb Co. (NYSE:BMY) was atypical in terms of stage and scope, but the biotech thinks the partnership validates its business model of in-licensing cancer compounds, doing development and then re-partnering the asset. The validation is nice to have as Aslan starts to line up for a Taiwanese IPO.

In 2011, BMS granted Aslan Asian rights to ASLAN002 (BMS-777607), a small molecule dual inhibitor of c-Met receptor tyrosine kinase (c-MET; MET; HGFR; c-Met proto-oncogene) and macrophage stimulating 1 receptor c-Met-related tyrosine kinase (MST1R; RON; CD136). The biotech then designed and completed a Phase I program.

Last week, Bristol-Myers paid Aslan $10 million up front to reacquire the Asian rights. The biotech is eligible for more than $50 million in milestones, plus royalties.

"We'd previously demonstrated we can in-license great compounds and develop them in Asia. The missing piece was: are companies willing to buy these back?" said CEO Carl Firth. "This is a nice demonstration to say the model works."

BMS did not disclose why it wanted the molecule back, but one potential reason is the work Aslan did to show the compound's effects on RON, an immune checkpoint target on macrophages.

"The c-MET activity we knew about and it's really the RON activity we've been learning about over the last few years," said Firth.

The compound is in Phase I testing in the U.S.

BMS pulled the trigger much earlier than Aslan is expecting from its partnerships, and also left the biotech with no rights to ASLAN002. Firth said Aslan usually wants to find partners for its assets after Phase II testing. Those partnerships are likely to be with third parties and not the originator company, he added.

The biotech also expects to retain some territorial rights.

But in terms of validating Aslan's model, Firth said, "this is close enough. The validation is all about whether we can take a molecule, bring it to Asia, target Asia-prevalent tumor types and create value."

Firth thinks the BMS deal was not a necessity for Aslan's plans to go public. "The market doesn't require a deal like this but it is certainly helpful," he said.

The company expects to file for a listing in Taiwan in about a month. After that, Taiwan's regulatory body will review the application and make a decision on whether Aslan can list, a process that typically takes four to six months.

Aslan's lead program, varlitinib, is in Phase II testing to treat cholangiocarcinoma, gastric cancer and breast cancer. Aslan has exclusive, worldwide rights to the oral small molecule pan-HER inhibitor from Array Biopharma Inc. (NASDAQ:ARRY).

— Steven Edelson

"THE MISSING PIECE WAS: ARE COMPANIES WILLING TO BUY THESE BACK?"

CARL FIRTH, ASLAN

DE-RISKING FIRST IN CLASS

Cleave Biosciences Inc. has steered clear of non-dilutive partnership dollars in hopes of internally validating the profile of its first-in-class cancer therapeutic CB-5083. Now, the biotech has attracted a cadre of new investors in last week's $37 million series B round, which should allow Cleave to generate clinical data for the selective inhibitor of valosin containing protein (VCP; p97) in a host of tumor types.

Celgene Corp. (NASDAQ:CELG) and Nextech Invest led the round and were joined by fellow new investor Arcus Ventures and existing investors 5AM Ventures, Clarus, New Enterprise Associates, OrbiMed Advisors, U.S. Venture Partners, Astellas Venture Management and Osage University Partners.

"WE WANT TO UNDERSTAND THE BREADTH OF ACTIVITIES BEFORE HANDING IT OVER."

LAURA SHAWVER, CLEAVE

CEO Laura Shawver noted that Celgene's participation in the tranched financing was purely financial. "We weren't looking to attach to a partner right now. We want to advance and demonstrate our molecule's validity and activity in multiple myeloma and other tumor subsets. We want to understand the breadth of activities before handing it over," she said.

CB-5083 is in Phase I testing for lymphoid hematologic malignancies such as MM, and for solid tumors. "The series B proceeds will let us finish off the Phase I dose escalation and expansion cohorts. That will take us to the next value inflection point in 2018," said Shawver.

The product is a first-in-class inhibitor of p97, a target that plays a key role in protein homeostasis by regulating the ubiquitin proteasome system. p97 sits upstream of the proteasome itself, which is the target of marketed drugs for MM.

"We like first in class but also look for ways to de-risk an investment," including working in a pathway that has produced approved therapies, said Nextech's Thilo Schroeder.

Cleave is the fourth investment that Nextech has made from its Oncology Fund IV, which closed at $64 million in July. "We need a sound set of clinical or preclinical data to validate a story," said Nextech's Alfred Scheidegger.

Cleave raised $44 million in its series A in 2011. Until last week, the company's only other financing was a $10 million addition to A round in 2013.

— Steve Edelson

FINESSE WITH LINZESS

Thanks to a relatively flat expense line in 2Q16, Ironwood Pharmaceuticals Inc. (NASDAQ:IRWD) almost doubled proceeds from its Linzess linaclotide deal with Allergan plc (NYSE:AGN). Going forward, the biotech expects to be able to deploy an expanding cash flow into its pipeline and to bring in additional products for its reps to sell.

Under a 2007 deal with Forest Laboratories Inc. (now part of Allergan), the companies equally split Linzess profits and expenses. "We wanted to make sure we would be in a situation not just taking a passive royalty in Linzess like you often see with biotech deals," said Tom Graney, Ironwood's CFO and SVP of finance and corporate strategy. "The team was confident Linzess was going to be an important, high-margin, highly profitable drug."

Linzess, which is marketed for irritable bowel syndrome with constipation (IBS-C) and chronic idiopathic constipation (CIC), posted 2Q16 sales of $150.5 million, up 34% from $112 million in 2Q15. Commercial costs and expenses dipped to $71.6 million from $77.8 million.

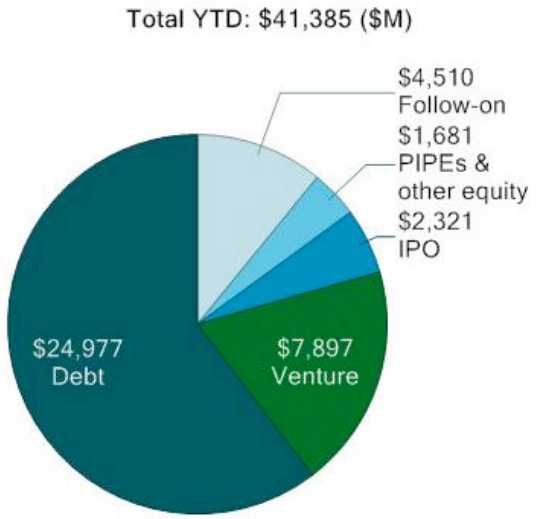
On Aug. 4, Ironwood reported $48.3 million in revenues from the Linzess collaboration in 2Q16, nearly double the $24.3 million recorded in 2Q15. The revenue figures include some reimbursement of Ironwood's SG&A expenses.

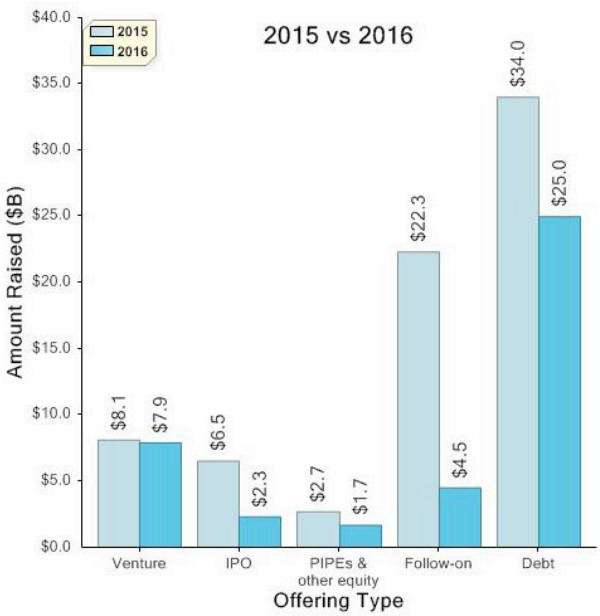
"The key message is that in 2020 we expect Linzess sales of more than $1 billion and we'll be spending about the same or not meaningfully more than we are now," said Graney.

The continued separation of revenue and expense curves should allow Ironwood to become cash flow positive in 2018. "That's an important

MONEY RAISED IN 2016

Last week, the biotech industry raised $48 million, bringing to $41.4 billion the total raised year-to-date. In 2015, a total of $108.8 billion was raised, including $54.8 billion in debt, $29.6 billion in follow-ons, $3.8 billion in PIPEs and other equity, $8.1 billion in IPOs, and $12.6 billion in venture capital. Totals include overallotments and warrants, and are rounded to the nearest millions.





milestone for investors, and we don't expect to need to access incremental capital before we get there," said Graney.

Ironwood is using the growing revenues to fund its next batch of Linzess products. A lower-dose version of the drug is under FDA review to treat CIC, while a second-generation colonic-release formulation is in Phase IIb testing to treat IBS-C. The company expects to report data this year.

The company also has found external opportunities. In April, Ironwood made an initial payment of $100 million to AstraZeneca plc (LSE:AZN; NYSE:AZN) to acquire U.S. rights to resistant gout drug Zurampic lesinurad. Ironwood expects to launch the approved product in October (see BioCentury, May 2). bc

— Steve Edelson

CORRECTION

U.S. Food and Drug Administration (FDA), Silver Spring, Md.

Business: N/A

An FDA review of all applications for new molecular entities from 2000-12, reported in *The Journal of the American Medical Association* in 2014, found that "uncertainties related to dose selection" was the most common reason for failing to obtain approval on the first submission (15.9%), followed by "choice of study end points that failed to adequately reflect a clinically meaningful effect" (13.2%). The Aug. 8 edition of *BioCentury* misstated which reason was most common.

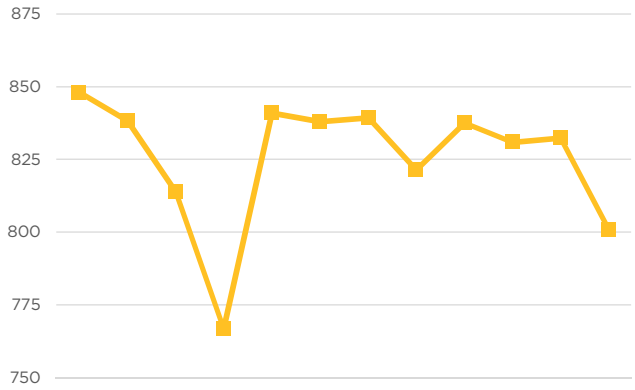
BIOCENTURY 100 PRICE & VOLUME TREND

Cumulative weekly performance of 100 bioscience stocks. 12-week period. Line shows Price Level change (Left scale. Index base=1000 on May 10, 1996). Bars show cumulative volume in millions (right scale).

BioCentury tracks 831 issues that report prices and volume daily. The BioCentury 100 is a subset used to monitor price and volume trends

BIOCENTURY LONDON INDEX

Weekly change in the combined market capitalization for 14 bioscience stocks listed on the LSE or AIM, 12-week period. Index base =1000 on May 10, 1996.



BIOCENTURY 100 INDICATORS

Week ended 8/12/16

PRICES
5384.86
dn 2%

VOLUME
1003.6M shrs
up 10%

PRICE GAINS

Stocks with greatest % price increase in the week ended 8/12. (Priced above $2; 5,000 minimum share volume)

Company	Ticker	$Close	$Chg	% Chg	Vol(00)
NovaBay	NBY	4.140	1.790	76%	23544
Mesoblast[1]	MESO	6.540	2.230	52%	93801
Endo[2]	ENDP	24.180	6.110	34%	774624
RegenxBio	RGNX	11.500	2.810	32%	7572
Prana[3]	PRAN	5.700	1.240	28%	2897813
MEI Pharma	MEIP	2.030	0.420	26%	132565
Kura Oncology	KURA	5.160	1.050	26%	64586
Eagle Pharmaceuticals	EGRX	62.050	12.510	25%	31050
Tonix	TNXP	2.560	0.490	24%	30892
Biomerica	BMRA	3.000	0.550	22%	1225
Aralez[2]	ARLZ	4.690	0.840	22%	44303
BioCryst	BCRX	5.040	0.900	22%	148980

PRICE DECLINES

Stocks with greatest % price decline (criteria as above).

Company	Ticker	$Close	$Chg	% Chg	Vol(00)
Concordia Healthcare[2]	CXRX	10.130	-6.280	-38%	217057
Carna	4572	¥1351.000	-¥729.000	-35%	23236
Check-Cap	CHEK	2.040	-0.990	-33%	26571
Nymox	NYMX	2.230	-1.070	-32%	123891
Myriad Genetics	MYGN	21.540	-8.920	-29%	314138
Array BioPharma	ARRY	3.530	-1.010	-22%	166744
Epizyme	EPZM	8.330	-1.990	-19%	33765
Editas Medicine	EDIT	20.110	-4.760	-19%	18684
Spectrum Pharmaceuticals	SPPI	5.810	-1.290	-18%	68568
Neos Therapeutics	NEOS	7.330	-1.470	-17%	7687
Sage Therapeutics	SAGE	36.710	-7.290	-17%	58223

VOLUME GAINS

Greatest changes in volume above 5,000 shares.

Company	Ticker	Vol(00)	%Chg	$Close	$Chg
Prana[3]	PRAN	2897813	4502%	5.700	1.240
Kura Oncology	KURA	64586	2365%	5.160	1.050
NovaBay	NBY	23544	1985%	4.140	1.790
Strongbridge Biopharma	SBBP	1447	1837%	4.300	0.060
Nymox	NYMX	123891	1503%	2.230	-1.070
Oncobiologics	ONS	923	1459%	3.640	0.160
Cyclacel	CYCC	32773	1373%	5.400	0.570
Mereo BioPharma	MPH	1470	856%	310.5p	26.5p
BiondVax[4]	BVXV	31889	847%	3.572	-0.028
Aldeyra Therapeutics	ALDX	8794	804%	5.760	-0.180

1 Includes volume from Australian Stock Exchange (ASX) and converted ADSs (1 ADS = 5 shares)
2 Includes volume from Toronto Stock Exchange (TSX)
3 Includes volume from ASX and converted ADSs (1 ADS = 60 shares)
4 Includes volume from Tel Aviv Stock Exchange and converted ADSs (1 ADS = 40 shares)

BIOCENTURY 100 ADVANCE-DECLINE TRENDS

Week ended	BC100 Price Level	BC100 Stocks gaining	Gaining vol. (00)	BC100 Stocks declining	Declining vol. (00)
Jul 15	5000.80	49	4295920	50	4664190
Jul 22	5165.37	73	4398101	27	2914313
Jul 29	5384.49	70	4809002	29	3593501
Aug 05	5501.39	61	6270413	39	2819196
Aug 12	5384.86	33	5400069	67	4636234

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NEWSROOM
pressreleases@biocentury.com

SAN CARLOS, CA
+1 650-595-5333; Fax: +1 650-595-5589
CHICAGO
+1 312-755-0798; Fax: +1 650-595-5589
WASHINGTON, DC
+1 202-462-9582; Fax: +1 202-667-2922
UNITED KINGDOM
+44 (0)1865-512184; Fax: +1 650-595-5589

Editor: Susan Schaeffer
Managing Editor: Jeff Cranmer
Senior Editors: Steve Edelson; Erin McCallister; Steve Usdin (Washington)
Associate Editor: Stephen Hansen

Senior Writer: Emily Cukier-Meisner
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BioCentury Inc.
BioCentury International Inc.

MAIN OFFICES
PO Box 1246
San Carlos CA 94070-1246
+1 650-595-5333; Fax: +1 650-595-5589

CORPORATE
Chairman: Karen Bernstein, Ph.D.
President & CEO: David Flores
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The 23rd Annual

NEWSMAKERS IN THE BIOTECH INDUSTRY

A Collaborative Gathering for the Corporate & Investment Communities
Showcasing Milestone-Rich Public Biotech Companies

September 9, 2016 • New York City

Your Access to BioPharma's Buy and Sellside Audience

Register Now – Seats are Limited and Filling Fast

NewsMakers is fertile ground for establishing relationships with the most active buy and sellside audiences in biopharma. Befitting BioCentury's 'Turf Neutral' format, *NewsMakers* allows all members of the professional investment community to attend, providing for maximum financial networking for all registrants. To date, we have more than 200 buysiders and 50 sellside analysts pre-registered. Sign up today and start setting up 1x1s to share your story with the Street.

Seating is limited and filling quickly, so register today.

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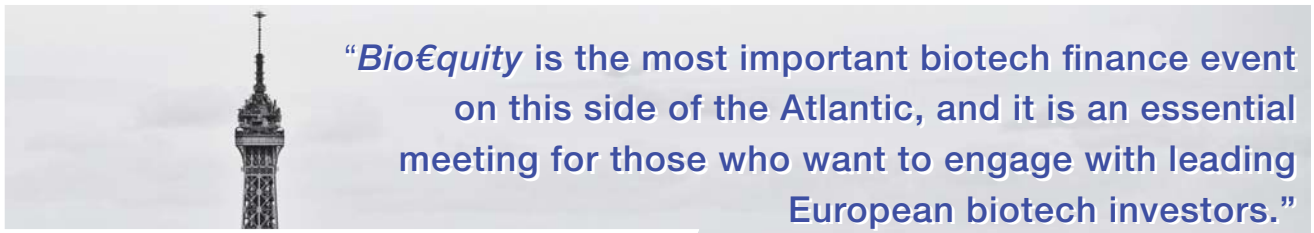
Supported by: Bio Biotechnology Innovation Organization

SELECTED PRE-REGISTERED BUYSIDERS

- Managing Director, **Advent Capital Management**
- Portfolio Manager, **Black Diamond**
- Portfolio Manager, **Citadel Global Equities**
- Healthcare Portfolio Manager, **E Squared Capital**
- Senior Research Analyst, **Essex Investment Management**
- Vice President, **JPMorgan Asset Management**
- Portfolio Manager, **QVT**
- CIO, **Sarissa Capital Management**
- Head, Healthcare Investments, **Yorkville Advisors Global**
- Managing Director, **Aisling Capital**
- Managing Director, **Bay City Capital**
- Director, Burroughs **Wellcome Fund**
- Managing Director, **Federated Kaufmann Fund**
- Investment Advisor, **HBM Partners**
- Principal, **JAFCO**
- Principal, **New Enterprise Associates**
- Managing Partner, **Nexus Life Science Partners**
- Partner, **Venrock**
- Director of New Ventures, **Yale University**

SELECTED PRE-REGISTERED SELLSIDERS

- Biotechnology Analyst, **Cowen and Company**
- Vice President, **FBR**
- SVP/Senior Biotech Analyst, **FBR & Company**
- Managing Director, **H.C.Wainwright**
- Managing Director, **Jefferies**
- Analyst, **JMP**
- Senior Analyst, **Laidlaw and Co.**
- Senior Biotech Analyst, **Maxim Group**
- Analyst, **Needham**
- Managing Director, **Piper Jaffray**
- Equity Research Analyst, **Raymond James**
- Senior Research Analyst, **Roth Capital Partners**
- Analyst, **SunTrust Robinson Humphrey**
- Managing Director, **Zacks**



"*Bio€quity* is the most important biotech finance event on this side of the Atlantic, and it is an essential meeting for those who want to engage with leading European biotech investors."

Dr. John Haurum, *CEO,* F-star

The 18th Annual

BIO€QUITY EUROPE 2017

BioCentury

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Bio Biotechnology Industry Organization

May 22-23, 2017 *Paris*

SAVE THE DATES

FOR BIOCENTURY'S UPCOMING CONFERENCES

BioCentury

The 24th Annual

FUTURE LEADERS IN THE BIOTECH INDUSTRY

April 7, 2017 *New York City*

New, Powerful Features Added to BCIQ

View Source Docs, Deal Maker Stats, Deal Flow and More

Building on the success of BCIQ 4, powerful functionality has been added to Deal Analyst. Now you can review source documents, create lists of top deal makers in particular areas, view deal flow by company, product and target and more.

SEND AN EMAIL TO TCAREY@BIOCENTURY.COM FOR
COMPLIMENTARY ACCESS

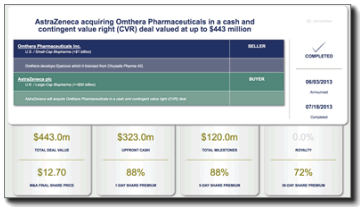
Pinpoint the Best Licensing and Investment Opportunities

This is the perfect time for you to assess BCIQ, BioCentury's online business intelligence tool. BCIQ integrates deal, pipeline, financial and company data on the biopharma industry into one, easy-to-use, web-based application that helps you discover and validate the best opportunities for your firm.

READ MORE

For a limited time we are offering you complimentary access to BCIQ. Better yet, our account management team will structure a deal that will make it easy for you to add BCIQ this month.

Send an email to tcarey@biocentury.com to get your complimentary access started.

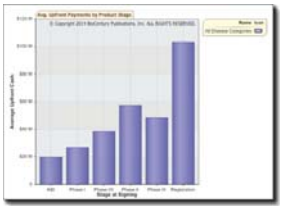


Content-Rich Deal Profiles; In-Depth Updates

BCIQ's simple and clean deal profiles provide you with a high level snapshot of the key metrics of a deal. Easily conduct a deep dive into the main aspects of the deal with BCIQ's powerful filtering tools.

Examine Deal Flow

Easily follow the flow of deals by company, product and target by linking to profile pages.



Export Deal Statistics & Charts

Quickly segment data by a variety of criteria and output tables and charts to fuel your analysis and presentations.

Review Source Documents

Source documents and press releases associated with deals are just a click away.

Create Top 10 Lists of Deal Makers

Easily create lists of the top deal makers by region, disease category, asset type and more.

Track Corporate Name Changes

BCIQ makes it easy to track company name changes across mergers and acquisitions.

SEND AN EMAIL TO TCAREY@BIOCENTURY.COM TO GET YOUR COMPLIMENTARY ACCESS STARTED.