

BioCentury

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INFECTIOUS ENTHUSIASM

BY EMILY CUKIER-MEISNER, SENIOR WRITER

After over two decades of scant effectiveness against cancer, oncolytic viruses could be close to finding their place in immuno-oncology combination regimens, where they could both be potentiated by and improve response rates to checkpoint agents. Meanwhile, the next generation of viruses may become more potent on their own by doubling as gene therapy vectors to enable tissue-specific delivery of therapeutic proteins and nucleic acids.

Companies have been studying oncolytic viruses since the 1990s, but only one has been approved in the U.S.

In the first decade of the 2000s, investment was steady but modest. But financings dramatically increased following the 2011 acquisition of [BioVex Inc.](#) by [Amgen Inc.](#) for \$425 million up front and up to \$575 in milestones.

The deal gave Amgen Imlygic talimogene laherparepvec (T-Vec), then in Phase III testing (see "The BioVex Effect," page 4).

BioVex learned from earlier attempts that may have blunted products' efficacy in an attempt to mitigate safety concerns related to administering a replicating virus. The company deliberately engineered Imlygic for improved potency on multiple fronts. Last year the modified herpes simplex virus type 1 (HSV-1) carrying the gene for GM-CSF became the first oncolytic virus therapy approved in the U.S.

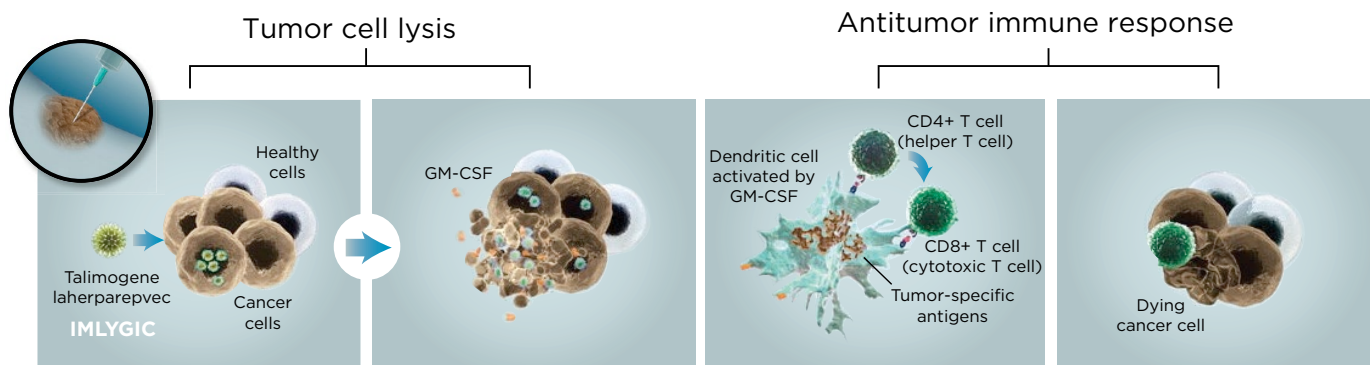
Though a game changer for the field of oncolytic viruses, Imlygic also illustrated how far the therapies still have to go to reach full potential, when patients with more advanced disease fared poorer than expected in its Phase III program.

Adding checkpoint agents to oncolytic viruses could be one way to improve responses in more patients, as it is now understood these agents may synergistically improve each other's efficacy in ways that could better address larger or more distant lesions. Most if not all oncolytic virus players plan to combine their therapies

TWO-PRONGED ATTACK

Oncolytic viruses can stimulate both direct and indirect killing of cancer cells, as illustrated by Imlygic talimogene laherparepvec (T-Vec) from **Amgen Inc.** (NASDAQ:AMGN). Imlygic is a modified herpes simplex virus type 1 (HSV-1) carrying the gene for GM-CSF. The modifications help the virus preferentially infect and replicate in cancer cells (first panel below). Replication leads to lysis and release of tumor-specific antigens, along

with GM-CSF (second panel). GM-CSF activates antigen-presenting cells, which present tumor antigens to helper T cells and cytotoxic T cells (third panel). In this way, the antigens act as an *in situ* vaccine to train the immune system to recognize the patient's cancer and mount a secondary attack (fourth panel). *Source: Amgen*



with checkpoint agents, and already a few pharma have started to test combinations.

Atlas Venture's Jason Rhodes said the VC chose to invest in oncolytic platform play **Replimune Ltd.** last year in part because of the expectation that the viruses will become hot commodities for combination regimens.

"Our view is anyone in the immuno-oncology space should have an oncolytic virus, and people may in fact want different ones, depending on what specific products they have in their portfolio," he said.

Oncolytic virus companies are also building on the idea that the viruses themselves can express proteins that complement their activity. In addition to delivering immunomodulatory proteins like GM-CSF, several companies are using viruses to deliver their own checkpoint agents, modify protein expression in tumors *in vivo*, or track viral spread and activity.

One major unresolved question is whether it is better to give the viruses locally or systemically. While systemic administration may be easier and doesn't require an accessible tumor, the virus must find its way to tumors and reach therapeutic concentrations before the immune system learns to recognize and disarm the invader.

PRECEDED BY CAUTION

An oncolytic virus preferentially infects cancerous cells over normal cells and kills the infected cancer cells by replicating within them, leading to lysis.

In the 1990s, **Onyx Pharmaceuticals Inc.** became the first company to engineer a virus meant to fight cancer. But Onyx's program showed little cell-killing activity, and the program was scuttled in 2003.

In 2005, China approved the first oncolytic virus, **Oncorine (H101)** from **Shanghai Sunway Biotech Co. Ltd.**, to treat head and neck cancer. Oncorine is a modified adenovirus with deletion of an E1B-55kd segment.

It would be another decade before Imlygic's approval in the U.S. One of the main challenges was an overabundance of caution about the safety of administering replicating viruses, according to **Oncolytics Biotech Inc.** Chairman, President and CEO Brad Thompson.

"People in the initial trials were quite cautious with the viruses, and may have overattenuated them because it wasn't known how safe it would be," said Robert Coffin, CEO of Replimune and founder and CTO of BioVex.

In fact the viruses have been generally well tolerated in the clinic, and the main challenge has been insufficient efficacy.

Another factor that may have limited the utility of early products is that a second mechanism by which oncolytic viruses attack cancer may have been underappreciated: following direct lysis of tumor cells, antigens freed from the tumor stimulate an immune response (see "Two-Pronged Attack").

In particular, it was not well understood that this second phase of response — in which the immune system learns to target the cancer — could play an important role in the duration and extent of response.

“Over the past 20 years, most people failed because they did not think they needed to promote the immune attack and monitor that for outcomes,” said [Targovax A/S](#) CMO Magnus Jäderberg.

ENLIGHTENED BY IMLYGIC

In contrast to many oncolytic viruses of its time, Imlygic was designed to increase the potency of both direct lysis and immune stimulation. The hope was to lyse locally injected regions and train the immune system to seek out and destroy distant tumors.

Coffin said he chose to work with HSV because it was thought to be more lytic than adenovirus. He looked for a wild strain because laboratory-derived ones tend to weaken over time as new generations replicate without the pressure to survive in human hosts. He said the winning strain — dubbed JS1 — came from the cold sore of a postdoctoral student in his [University College London](#) lab.

Coffin improved the selectivity and oncolytic potency of the virus by deleting the genes encoding ICP34.5 and ICP47 and adding a mutation to increase expression of US11. He improved immunogenicity by inserting the gene for GM-CSF.

“We haven’t tested the virus without GM-CSF in humans, but presume that was part of the reason T-Vec turned out to be as effective as it did,” he said.

In its Phase III program in patients with unresectable melanoma, Imlygic produced a significantly higher durable response rate than GM-CSF (15.6% vs. 1.4%, $p < 0.0001$), and barely missed significantly improving overall survival (OS) (23.3 months vs. 18.9 months, $p = 0.051$).

A subgroup analysis suggested that Imlygic worked much better for patients whose disease hadn’t spread beyond the skin. Median OS for patients whose cancer had not progressed beyond skin or lymph nodes was 19.6 months longer in the Imlygic group than in the GM-CSF group; for patients with metastases to lung and other viscera, median OS was 2.5 months shorter in the Imlygic group.

Coffin said several factors could contribute to why visceral metastases didn’t appear to respond to Imlygic as much as skin lesions. The stimulated immune response might not be sufficient to attack larger tumors, or the visceral tumors may have better defense mechanisms.

Amgen SVP of Translational Sciences David Reese said the company expects Imlygic’s “real utility” will be in combination regimens, such as with checkpoint inhibitors.

The biotech has several combination studies ongoing. Amgen is collaborating with [Merck & Co. Inc.](#) on a Phase III study of Imlygic plus the pharma’s Keytruda pembrolizumab in patients with metastatic melanoma.

And in June 2015 Amgen partnered with [Roche](#) for a Phase IIb study of Imlygic plus Roche’s atezolizumab (MPDL3280A) to treat triple-negative breast cancer and colorectal cancer with liver metastases.

Keytruda is a humanized IgG4 mAb against PD-1 approved to treat melanoma and non-small cell lung cancer (NSCLC). Atezolizumab is a human mAb against PD-L1. Roche and its [Genentech Inc.](#) unit plan to submit regulatory applications for atezolizumab to treat bladder cancer this year.

BETTER TOGETHER

All 14 companies that spoke to BioCentury said they are testing or intend to test oncolytic viruses in combination with checkpoint inhibitors in the clinic.

Checkpoint inhibitors could help overcome immunosuppression in the tumor microenvironment that allows cancer to resist or evade the immune attack precipitated by an oncolytic virus. And oncolytic viruses can have a secondary effect of up-regulating checkpoints like PD-1 when they trigger cellular defense mechanisms.

“OUR VIEW IS ANYONE IN THE IMMUNO-ONCOLOGY SPACE SHOULD HAVE AN ONCOLYTIC VIRUS.”

JASON RHODES, ATLAS

“We think PD-1 antibodies are the ready-made solution — they’re made to go together,” said [Virttu Biologics Ltd.](#) CSO Joe Conner.

Coffin added that oncolytic viruses also may improve responses to checkpoint therapies by releasing patient-specific neoantigens when they lyse tumors. “If checkpoint blockade doesn’t have anything from which to release the brakes, it could be why the majority of patients don’t respond,” he said.

Rhodes noted that synergistic and safe combination with checkpoint inhibitors with low liability for additional toxicity was important for Atlas’ choice to invest in the oncolytic space.

“It’s not just layering two agents. You have neoantigen presentation in a highly immunogenic way that’s very safe,” said Rhodes.

The potential of checkpoint inhibitors to form the backbone of combination therapies in a variety of cancers has led pharmas to license oncolytic viruses as potential components of those cocktails, or engage in R&D collaborations with biotechs developing viruses.

In January 2015 [Omnis Pharma Inc.](#) granted [AstraZeneca plc’s](#) [MedImmune LLC](#) unit rights to develop and commercialize Omnis’ engineered strain of vesicular stomatitis virus (VSV) expressing interferon (IFN) beta. The virus is in Phase I testing to treat hepatocellular carcinoma (HCC).

David Berman said MedImmune plans to combine the virus with molecules in its immunotherapy portfolio, though he declined to say which ones. Berman is SVP and head of the oncology innovative medicines unit at MedImmune.

He said MedImmune chose Omnis’ VSV product over other oncolytic viruses because preclinical data suggest VSV has “the optimal combination of innate immune stimulation and oncolytic killing for use in combination with checkpoint inhibitors.”

Berman said the IFN beta gene improves selectivity for cancer cells by triggering antiviral immunity in normal cells to prevent their infection, whereas tumor cells often have defects in the pathway so it would not benefit.

In 2009 researchers at the [Mayo Clinic](#) published in *Cancer Research* that VSV expressing IFN beta lysed murine mesothelioma cells *in vitro* and regressed tumors arising from the same cell line in mice. Tumor regression was enhanced by the presence of CD8+ T cells. The presence of IFN beta increased safety and protected immune-deficient mice from lethal neurotoxicity.

Merck also is developing other combinations with Keytruda in addition to its work with Amgen. In 2015 Merck began a collaboration to combine Keytruda with [DNAtrix Inc.](#)'s DNX-2401 in a Phase II study to treat recurrent glioblastoma. A second 2015 collaboration, with [Viralytics Ltd.](#), is adding the biotech's Cavatak to Keytruda in a Phase Ib trial in patients with advanced NSCLC or metastatic bladder cancer. DNX-2401 is a genetically modified oncolytic adenovirus that uses arginine-glycine-aspartic acid (RGD)-binding integrins to enter and replicate in tumor cells. Cavatak is a formulation of coxsackievirus A21 (CVA21).

Executive Director of Oncology Clinical Research David Kaufman said Merck sees oncolytic viruses as a way to create an off-the-shelf product that can produce effects similar to a personalized cancer vaccine.

He said Merck chose its partners after clinical data showed the viruses could regress tumors.

In addition to Keytruda, Merck hopes to test the combination of oncolytic viruses with agents in its pipeline that target immune proteins in the tumor microenvironment.

One example Kaufman gave is MK-4166, a mAb targeting the immunostimulatory checkpoint glucocorticoid-induced tumor necrosis factor receptor (TNFR)-related protein (GITR; TNFRSF18).

"It's essentially a double shot on T cell priming — release the antigen in an immunogenic way, then co-stimulate the T cells," he said.

I'M YOUR VEHICLE

Some companies are going one step beyond co-administration and using viruses as vectors to deliver proteins other than GM-CSF to boost the immune response, modify a tumor's own cells, or track the progress of the therapy.

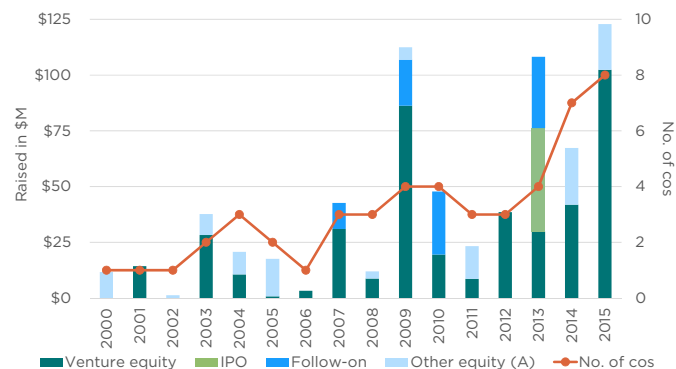
[Oncolys BioPharma Inc.](#) has oncolytic viruses in preclinical testing that express interfering RNAs, immunoproteins or tumor suppressors like p53, according to President and CEO Yasuo Urata.

Meanwhile, newco [Turnstone Biologics Inc.](#) is using its viruses to deliver cancer antigens so they can simultaneously act as oncolytics and vaccines, which the company expects will increase response rates and the strength of the immune response.

"There will be patients who are mostly impacted by the oncolytic properties of our virus, and there will be patients mostly impacted by the T cell vaccine side of our vector. We expect the bulk of the patients will fall in the middle — both infecting tumors and also driving a T cell

THE BIOVEX EFFECT

In the last five years, oncolytic virus companies raised \$360.2 million via equity offerings, topping the \$321.5 million raised in 2000-10. The catalyst of renewed attention to the space was the early 2011 acquisition of BioVex Inc. by [Amgen Inc.](#) (NASDAQ:AMGN). BioVex was also the reason for the spike in financings in 2009, when the company raised a \$70 million round, accounting for 81% of venture investment and 62% of the total. (A) Includes PIPEs, rights offerings and warrant exercises; Source: *BCIQ: BioCentury Online Intelligence*



response — and we know from our model that's where it works best," said Turnstone CTO Brian Lichty.

The company's most advanced product is an oncolytic Maraba virus engineered to express melanoma-associated antigen A3 (MAGEA3) in Phase I/II testing for advanced or metastatic solid tumors that express the antigen.

Several companies have preclinical programs that use the viruses to deliver their own immunotherapy combination partners, such as anti-PD-1 mAbs.

Virttu CEO Deirdre Gillespie said oncolytic virus companies wouldn't have to develop new proprietary mAbs to do so.

"We have next-generation products with additional genes and secured IP even though the protein is well known, because of the way we incorporated it. We think it's a clear IP route for novelty," she said.

Gillespie declined to say whether this might include marketed checkpoint agents like Keytruda, but did say Virttu is exploring next-generation viruses that express single chain antibodies for targeting.

Another tack is using an oncolytic virus to deliver gene therapy directly to tumor cells.

DNAtrix is studying a preclinical version of DNX-2401 that contains the co-stimulatory molecule OX40 ligand (OX40L; CD134L).

CEO Frank Tufaro said expressing the ligand on tumor cells puts the checkpoint agent right where it is biologically needed.

"First it gets expressed on the tumor cell surface, and it will then be released when the cells die — we get both kinds of effects," he said.

And **PsiOxus Therapeutics Ltd.** has a preclinical program to express an undisclosed molecule on tumors that can engage and activate T cells.

CEO John Beadle said the tumors themselves are taught to engage T cells — not the other way around. Furthermore, the modification takes place *in vivo*, and doesn't require prespecifying an antigen.

“We’re actually modifying the tumor, so it doesn’t matter what the T cell recognizes — it can engage directly with the tumor,” he said.

DELIVERY DILEMMA

One unresolved question is whether to deliver oncolytic viruses systemically or as direct injections into tumors.

Systemic delivery is easier to administer, does not depend on a secondary immune response to attack distant lesions, and could be used to treat liquid cancers or solid tumors that are difficult to access with a needle. But viruses are targets for the immune system, and patients who do not already have neutralizing antibodies from natural exposure to a virus can develop them during treatment.

ONCOLYTIC PIPELINE

At least 19 oncolytic viruses are in clinical development. For products in development for multiple indications, the status of the lead indication is shown. Many viruses are now being studied in combination with other classes of therapeutics that can potentiate their effects or change the ways the viruses interact with cancer cells. The pipeline below shows combinations with checkpoint inhibitors in purple, targeted therapies in green, adenoviral priming in yellow and chemotherapy in light blue. Monotherapy programs are in dark blue.

The chart below excludes virus combination products where the virus is not inherently oncolytic. Also excluded are two oncolytic HSV programs that **Amgen Inc.** (NASDAQ:AMGN) obtained through its acquisition of Catherex Inc. The programs are in Phase I/II testing but are not listed in Amgen's pipeline. (A) Phase I study included interferon (IFN) gamma, but the company is no longer pursuing this combination; (B) Phase I study was conducted as monotherapy; company plans to study combination with Avastin bevacizumab in Phase I/II. Sources: *BCIQ: BioCentury Online Intelligence, ClinicalTrials.gov, company press releases and websites*

COMPANY	PRODUCT	PH I	PH II	PH III
Cold Genesys	CG0070	Bladder		⌵ Compl Ph III 2019
SillaJen / Green Cross / Lee's Pharma / Transgene	Pexa-Vec pexastimogene devacirepvec	Liver		⌵ Compl Ph III 2019
Oryx	ParvOryx	Brain		⌵ Compl Ph I/II pancreatic cancer 2016
Perceiver	NTX-010	Lung		⌵ NA
Oncolys / Medigen	Telomelysin	Liver	⌵ Compl Ph I/II 2018	
Oncolytics / Andrus Reo	Reolysin pelareorep	Multiple myeloma	⌵ Start Ph III 2016	
PsiOxus	Enadenotucirev	Ovarian, epithelial	⌵ Compl Ph I/II 2017	
Takara	HF10	Melanoma	⌵ Compl Ph II 2016	
Targovax	ONCOS-102	Mesothelioma	⌵ Interim Ph I/II data 1H17	
Viralytics	Cavatak	Melanoma	⌵ Compl Ph II extension 2016	
Virttu	Seprehvir	Mesothelioma	⌵ Compl Ph I/II 2016	
DNAtrix	DNX-2401	Brain (A)	⌵ Compl Ph I w/ temozolomide 2017	
Genelux	GL-ONC1	Ovarian (B)	⌵ Start Ph I/II 1H16	
Shanghai Sunway	H103	Head and neck	⌵ NA	
AstraZeneca / Omnis	Vesicular stomatitis virus	Liver	⌵ NA	
MultiVir	Ad-VirRx 007	Solid tumors	⌵ NA	
SillaJen	JX-929	Solid tumors	⌵ NA	
Turnstone	Oncolytic Maraba virus	Solid tumors	⌵ Start Ph II portion of Ph I/II 1Q17	
VCN Biosciences	VCN-01	Solid tumors	⌵ Compl Ph I 2016	

“The objective of inducing a very potent immune response to the tumor without inducing a potent immune response to the virus itself is incompatible. As a result, after the first dose, any patient will be strongly positive against the virus,” said Coffin.

In addition, once delivered, the virus has to achieve high enough concentrations in the right place to be effective. Jäderberg said oncolytic viruses often accumulate in the liver, where they are subsequently metabolized.

According to Reese, Imlygic is given by intratumoral injection to avoid the problem of neutralizing antibodies. But Amgen is still interested in finding a way to deliver oncolytic viruses systemically to treat cancers that lack easily accessible lesions.

Reese wouldn't elaborate on Amgen's approach for systemic delivery, other than to say the company isn't limiting itself to HSV.

The choice of viral species can make a big difference in whether and when neutralizing antibodies develop, and how easily the virus can be given systemically.

Conner said viruses that are widely prevalent in humans — such as HSV — have often evolved techniques to evade immune surveillance. “Even with antibodies and T cells, you still get cold sores,” he noted.

On the other hand, viruses that are not widely prevalent in humans are unlikely to encounter much preexisting immunity.

Turnstone scientific co-founder John Bell said there is little natural immunity to the Maraba virus, which was isolated from sand flies in Brazil. Bell is a senior scientist at the [Ottawa Hospital Research Institute](#) and a professor at the [University of Ottawa](#).

Lichty said Maraba tends to preferentially accumulate not in the liver, but in the spleen in a compartment where it is exposed to antigen-presenting cells, which could help it induce an immune response.

“If you give it intravenously to an animal with a tumor, it shows up in two places: the spleen, where it can't replicate but does express proteins transiently, and the tumor, where it's amplified. You soon wind up with a biodistribution that's tumor-exclusive,” he said.

The viruses can still be effective in the context of neutralizing antibodies, so long as they persist long enough to train the immune system to recognize and attack the cancer.

Turnstone's Phase I/II program is testing the MAGEA3-expressing Maraba virus with and without immunologic priming with an adenoviral vaccine that also expresses MAGEA3.

THE LOCAL OPTION

Companies exploring non-systemic delivery options are evaluating various methods to improve activity against distant or hard-to-reach tumors.

Viralytics is testing systemic, intratumoral, and intravesicular delivery of Cavatak. Managing Director and CEO Malcolm McColl said Viralytics is looking to optimize the dosing regimen for Cavatak to spark the secondary immune response with a limited number of doses.

ONCOLYTIC DUOS AND DX

Several companies are looking for therapeutic combinations that change how oncolytic viruses interact with cancer cells.

At least two companies, [Oncolys BioPharma Inc.](#) and [Oryx GmbH & Co. KG](#), are investigating co-administering the therapies with HDAC inhibitors.

Oncolys President and CEO Yasuo Urata said HDAC inhibitors increase tumor cells' ability to uptake Telomelysin (OBP-301) via the coxsackie adenovirus receptor (CAR).

“After dosing the HDAC inhibitor, the tumor cell expresses the CAR much more,” he said.

Similarly, [Genelux Corp.](#) is using [Roche](#) and [Genentech Inc.](#)'s Avastin bevacizumab to increase tumor uptake of GL-ONCI (GLV-1h68).

Genelux President and CEO Thomas Zindrick said the humanized mAb against VEGF permeabilizes tumor vasculature, which increases viral distribution and augments immunostimulation.

GL-ONCI is a genetically stable modified vaccinia virus that incorporates green fluorescent protein (GFP) to enable companion imaging. It is in Phase I/II testing to treat platinum-resistant ovarian cancer.

Zindrick said Genelux initially studied vaccinia virus as a cancer diagnostic platform, but chose to focus on therapeutic uses of the virus after seeing its potential for activity in animal models. The company has not ruled out developing diagnostics in the future.

Oncolys is doing both: it is developing a version of its therapeutic oncolytic virus Telomelysin as a laboratory test to detect circulating tumor cells in peripheral blood. TelomeScan (OBP-401) is an adenovirus encoding the human telomerase reverse transcriptase (hTERT) promoter and GFP. TelomeScan replicates in cells with high telomerase activity, which is common in cancer cells but rare in normal cells.

In November 2015 Oncolys granted [Liquid Biotech USA Inc.](#) exclusive rights to develop and commercialize TelomeScan in North America. Chairman, President and CEO Philip Sass said the company has studied TelomeScan in the clinic to detect lung cancer, bladder cancer and glioma, and in early 2017 plans to begin a study to support a 510(k) submission.

— EMILY CUKIER-MEISNER

“What we're looking to achieve is not necessarily massive tumor debulking. We're looking for the virus to track to the tumor, replicate, get the immune response up and running in those tumors, then follow up with checkpoint inhibitors,” he said.

Jäderberg added that local delivery could reduce the chances of side effects from transgenes like GM-CSF.

Potency is also a factor in being able to give a virus intratumorally — since physicians and patients may object to repeated injections at tumor sites that are painful to access, like the lung, or difficult to deliver to safely, like the brain.


“For lesions deep in visceral sites, it may be possible to reach them by interventional radiology, endoscope or bronchoscope, but you’re really limited in how many times you can do that,” said Kaufman.

Kaufman said one reason Merck chose to collaborate with DNATRIX is because DNX-2401 showed clinical activity in glioblastoma in a single dose.

DNX-2401 is delivered to glioblastoma intratumorally using the MEMS Cannula (AMC) targeted delivery platform. In May 2015 DNATRIX licensed exclusive rights to use AMC to treat brain cancer from [Alcyone Lifesciences Inc.](#)

“If they had to give five or six doses by that route, that would be unfeasible despite the unmet medical need. But if a single dose and administration show clinical benefit, then that’s a promising path forward,” Kaufman said.

Coffin said Replimune hopes to get sufficient potency for intratumoral administration by using the virus to deliver proteins that enhance the virus’ lytic and immunostimulatory capabilities. He declined to give details.

“If you only have to inject a small number of tumors a small number of times, it opens the way to treating any type of cancer — and suggests while IV administration might be nice, it’s not essential,” he said. 

COMPANIES AND INSTITUTIONS MENTIONED

Alcyone Lifesciences Inc., Lowell, Mass.
Amgen Inc. (NASDAQ:AMGN), Thousand Oaks, Calif.
AstraZeneca plc (LSE:AZN; NYSE:AZN), London, U.K.
DNATRIX Inc., Houston, Texas
Genelux Corp., San Diego, Calif.
Genentech Inc., South San Francisco, Calif.
Liquid Biotech USA Inc., Audubon, Pa.
Mayo Clinic, Rochester, Minn.
MedImmune LLC, Gaithersburg, Md.
Merck & Co. Inc. (NYSE:MRK), Kenilworth, N.J.
Omnis Pharma Inc., Rochester, Minn.
Oncolys BioPharma Inc. (Tokyo:4588), Tokyo, Japan
Oncolytics Biotech Inc. (TSX:ONC; OTCQX:ONCYF), Calgary, Alberta
Oryx GmbH & Co. KG, Baldham, Germany.
Ottawa Hospital Research Institute, Ottawa, Ontario
PsiOxus Therapeutics Ltd., Abingdon, U.K.
Replimune Ltd., Oxford, U.K.
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
Shanghai Sunway Biotech Co. Ltd., Shanghai, China
Targovax A/S, Lysaker, Norway
Turnstone Biologics Inc., Toronto, Ontario
University College London, London, U.K.
University of Ottawa, Ottawa, Ontario
Viralytics Ltd. (ASX:VLA; OTCQX:VRACY), Pymble, Australia
Virtu Biologics Ltd., Glasgow, U.K.

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EMERGING COMPANY PROFILE

HERCULES' IDO ALTERNATIVE

BY STEPHEN HANSEN, ASSOCIATE EDITOR

Hercules Pharmaceuticals B.V. is developing an inhibitor of aryl hydrocarbon receptor that taps into the same pathway as IDO and TDO inhibitors but could improve upon their tolerability while delivering similar efficacy. Improved tolerability could be a benefit when used in combination with other immunotherapies.

According to CEO Bart Wuurman, aryl hydrocarbon receptor (AHR) is a key component of the tryptophan metabolism signaling pathway, which includes indoleamine 2,3-dioxygenase (INDO; IDO) and tryptophan 2,3-dioxygenase (TDO2; TDO).

In cancer, both IDO and TDO mediate tryptophan catabolism to generate kynurenine, which in turn leads to chronic activation of AHR. Activated AHR increases Treg activity in the tumor environment, suppressing the antitumor immune response.

At least eight companies are developing inhibitors of IDO or TDO, with at least five candidates in the clinic. The lead compounds are in Phase II testing and have reported encouraging early data.

In November, [Incyte Corp.](#) reported Phase I/II data for the IDO1 inhibitor epacadostat that showed a disease control rate of 74% and an objective response rate (ORR) of 53% in 19 evaluable melanoma patients who also received [Merck & Co. Inc.](#)'s anti-PD-1 mAb Keytruda pembrolizumab.

Last month, [NewLink Genetics Corp.](#) reported Phase Ib/II data from 12 evaluable metastatic pancreatic cancer patients that showed the IDO inhibitor indoximod led to an ORR of 42% when given in combination with gemcitabine and [Celgene Corp.](#)'s Abraxane nab-paclitaxel.

Epacadostat and indoximod were well tolerated, but Wuurman thinks an AHR inhibitor could be even better tolerated. The reason is that IDO and TDO are widely expressed in many

HERCULES PHARMACEUTICALS B.V.

Amsterdam, the Netherlands

Technology: Small molecule inhibitors of aryl hydrocarbon receptor (AHR)**Disease focus:** Cancer**Clinical status:** Preclinical**Founded:** 2013 by David Sherr and Drug Discovery Factory (DDF)**University collaborators:** [Boston University](#)**Corporate partners:** None**Number of employees:** 3**Funds raised:** None**Investors:** None**CEO:** Bart Wuurman**Patents:** None

healthy and malignant tissues, while AHR is 50x overexpressed in tumor cells compared with normal tissue. Wuurman said *in vitro* data have shown the more aggressive the tumor type, the higher the expression levels of AHR.

He noted that a better tolerability profile may be particularly important in combination studies with immunotherapy drugs that have their own significant toxicities, such as [Bristol-Myers Squibb Co.](#)'s Yervoy ipilimumab. Yervoy's label includes a black box warning for immune-mediated adverse reactions, including hepatotoxicity.

Hercules has not yet published preclinical data for its lead AHR inhibitor, CB7993113. But according to co-founder and CSO David Sherr, the compound has shown no signs of toxicity in a highly sensitive embryo zebrafish model and in mouse xenograft models of various cancer types treated with increasing doses over a six-week period.

Sherr added that data from a mouse xenograft model of oral cancer showed that 90% of

animals treated with CB7993113 survived vs. only 25% of animals treated with placebo at 28 days.

"In some of these experiments we are doing xenografts of tumors where mice actually begin to gain weight toward the end as the tumor gets under control," he said.

He said additional preclinical data show that inhibiting AHR can resensitize tumors to traditional chemotherapy, block cancer cell metastasis and prevent the generation of cancer stem cells.

Hercules is funding preclinical development with €3.5 million (\$3.8 million) in European grants.

The biotech is aiming to raise at least €14 million (\$15.2 million) in a series A round to fund development through Phase IIa testing. The company expects CB7993113 to enter the clinic next year for triple-negative breast cancer, oral cancers, glioblastoma or pancreatic cancer.

Wuurman said he isn't aware of any other companies developing an AHR inhibitor. The company licensed exclusive, worldwide rights to CB7993113 from [Boston University](#), which received an equity stake in Hercules in the deal. [bc](#)

COMPANIES AND INSTITUTIONS MENTIONED

[Boston University](#), Boston, Mass.[Bristol-Myers Squibb Co.](#) (NYSE:BMJ), New York, N.Y.[Celgene Corp.](#) (NASDAQ:CELG), Summit, N.J.[Hercules Pharmaceuticals B.V.](#), Amsterdam, the Netherlands[Incyte Corp.](#) (NASDAQ:INCY), Wilmington, Del.[Merck & Co. Inc.](#) (NYSE:MRK), Kenilworth, N.J.[NewLink Genetics Corp.](#) (NASDAQ:NLNK), Ames, Iowa

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REGULATION

OFF-LABEL OPTIONS

BY STEVE USDIN, WASHINGTON EDITOR

Bringing FDA's oversight of communications about off-label uses of medical products into compliance with the courts' interpretation of constitutional protection of speech will be one of FDA Commissioner Robert Califf's more pressing and difficult challenges. The Duke-Margolis Center for Health Policy, a new think tank directed by former CMS Administrator and FDA Commissioner Mark McClellan, released a white paper last week that could help.

Policy Options for Off-Label Communication: Supporting Better Information, Better Evidence, and Better Care notes that the courts have rejected several attempts to enforce restrictions on off-label communication. The result has been "an unsatisfactory and unsustainable patchwork of regulations, guidance documents, and agency practices related to off-label communication, product labeling, and scientific exchange of information," according to the white paper.

"To promote the public health you need to have adequate information out there to support off-label uses, and that creates a need for FDA's regulatory scheme to allow manufacturers to have alternative channels to provide off-label information," Coleen Klasmeier, a partner at Sidley Austin LLP and former FDA staff attorney, said at a Duke-Margolis Center meeting last week.

Klasmeier served on the working group that wrote the report.

The report presents a menu of options because the working group could not come to consensus on a single path forward. It proposes that policymakers consider rethinking product labels to find space for real-world evidence, and suggests creating an independent external body that could make recommendations on some kinds of off-label communications.

In addition to these major policy changes, the document outlines short-term steps FDA could take to clarify its off-label policies, including issuing guidance documents and aggregating its policies on a single web page.

EXPANDING THE LABEL

The white paper suggests two approaches to revising FDA's regulation of efficacy claims or labels to allow companies to communicate data that do not meet current labeling standards.

"One approach could be to maintain the current high standards for incorporating evidence within labeling itself, but with a much clearer recognition that lower levels of supporting evidence can be communicated within certain circumstances or to particular audiences — effectively allowing for a broader scope of communication that uses the labeling and additional 'sanctioned' evidence as its foundation," the paper suggests.

The other proposal would be a more radical departure from tradition. It envisions "introducing additional, clearly-delineated tiers of evidence into the product labeling: primary efficacy claims and information for an approved indication would be given the most weight and highest placement, but additional evidence with appropriate qualifications could

be added to the labeling as a greater body of evidence is generated on the product's use in different contexts."

The white paper acknowledges that oversight of a wide range of off-label communications could "represent a substantial additional administrative burden for the FDA." It suggests that this burden could be lightened by empowering an independent external body to accredit certain types of communication, an idea that did not receive "universal support" from the working group that wrote the report.

"TO PROMOTE THE PUBLIC HEALTH YOU NEED TO HAVE ADEQUATE INFORMATION OUT THERE TO SUPPORT OFF-LABEL USES."

COLEEN KLASMEIER, SIDLEY AUSTIN

"This organization could focus its efforts on reviewing sponsor evidence and associated communications about off-label use, and approve them for broader distribution," according to the white paper. "Approval could be given within a rank, score, or grade system that confers greater weight to better evidence, and could be given contingent upon continued evidence generation and resubmission to the clearing body."

The proposed body would make recommendations that would not be legally binding on FDA, and companies would not be compelled to submit proposed communications for review.

"Incentives in the form of more rapid and predictable review and action would need to be in place to encourage sponsors to develop evidence and submit communication materials," the white paper proposes. "The end goal would be a process that augments the FDA's capacity to review evidence and communications based on it, does not change FDA's ability to pursue enforcement action, and allows for a potential diversity of communication types reflective of rapidly emerging evidence."

DIAGNOSING THE PROBLEM

PhRMA EVP and General Counsel Mit Spears said that while the Duke-Margolis Center paper does a good job of making the public health case for improving off-label communications policies, it "dances around" the single most important issue: how FDA defines the "truthful and non-misleading" standard the courts have set for corporate free speech.

“I DON’T THINK YOU CAN RESOLVE THE ISSUE WITHOUT RESOLVING THE QUESTION OF WHAT CONSTITUTES TRUTHFUL AND NON-MISLEADING INFORMATION.”

MIT SPEARS, PhRMA

“I don’t think you can resolve the issue without resolving the question of what constitutes truthful and non-misleading information,” Spears said. “That’s up to FDA or the courts to decide, and we think it is much better if it is FDA.”

He told BioCentury there is a danger that courts could back FDA into a corner, mandating communications policies that comply with the First Amendment to the U.S. Constitution, but that don’t take all of the nuances of public health into consideration.

“If a regulatory solution is not forthcoming, the courts will continue to be asked to intervene,” he said. “The field of choices will start getting limited by court decisions that are perhaps not particularly well thought out.”

Spears feels that achieving a workable regulatory solution will require “fine-tuning” that is beyond the courts’ expertise, for example tailoring the kinds of information that can be communicated to the sophistication of the audiences. Spears and PhRMA did not participate in the Duke-Margolis Center working group.

Jeff Francer, VP and senior counsel at PhRMA, told BioCentury FDA could create a regulation “defining what is misleading if information is provided outside of labeling.” The regulation could require that companies provide physicians with information on how studies were designed and analyzed, and require that companies provide studies that they may disagree with, he suggested.

Speaking at the Duke-Margolis Center meeting, Peter Pitts, president of the Center for Medicine in the Public Interest, also warned that the courts or Congress could take the off-label policy debate in directions that could be bad for public health.

“Unless FDA steps up to the plate to lead this conversation, but also looks to outside advisors to help it formulate its viewpoints, we are all going to be sucked into a very unpleasant vortex,” he said.

Pitts was a member of the working group and an author of the report.

The courts are not the only source of pressure for FDA to change its off-label policies. The white paper notes a “growing emphasis on value and on payment and coverage mechanisms that are linked to evidence and results,” including evidence that is not on product labels and that is difficult for manufacturers to discuss under FDA’s current regulations.

According to the paper, clinicians are increasingly turning to real-world evidence “that often does not reach the level of certainty needed for inclusion on the product labeling.”

Additionally, the paper notes, the “evolution of patients as equal partners in their own treatment decisions creates further needs related to off-label communication involving non-professional audiences.”

COURTING OFF-LABEL POLICY

Official FDA statements about changes to off-label policy will have to wait for the dust to settle on Calif’s confirmation, and possibly for the settlement of litigation [Amarin Corp. plc](#) brought against FDA’s attempts to prevent truthful, non-misleading off-label promotion of Vascepa icosapent ethyl.

The U.S. District Court for the Southern District of New York granted Amarin a preliminary injunction, and settlement talks are under way. The government is due to inform the court of the progress of the negotiations by March 18.

In the meantime, speaking at last week’s Duke-Margolis forum, Joshua Sharfstein, associate dean at the Johns Hopkins Bloomberg School of Public Health, articulated the views of some agency officials who have resisted major changes to off-label policies. Sharfstein is former FDA principal deputy commissioner. He was not an author of the report, but he did provide the working group with feedback on a draft of the report.

The problem, he said, is judicial activism, not FDA’s policies. “Judges are taking over FDA roles in assessing whether something is inaccurate or misleading, and if they are doing that, there is no line that FDA can draw that a judge won’t say ‘actually I think this isn’t misleading,’” he said.

Sharfstein’s solution is simple, if not realistic: “I think it is very important for companies to stand down in suing the FDA.”

He also called for the public health community to admonish judges against making determinations about the veracity of specific communications about off-label uses of medical products. “It is very important to send a message to judges that they are playing with matches,” he said.

Communications from manufacturers about off-label uses of approved drugs are suspect, he said, because companies have a history of distorting science in ways that endanger patient health.



COVER STORY

IRONWOOD'S BRAINY IDEA

Ironwood's preclinical group is lining up AD and vascular dementia as the next indications to explore with the company's sGC platform.

STRATEGY

CHANGING THE CHANNEL

Researchers can now publish their attempts to reproduce each other's data on a new channel that's the brainchild of leaders from Amgen and F1000.

TARGETS & MECHANISMS

BORROWING FOR ZIKA

While companies and agencies chase traditional routes to a Zika vaccine, some groups are borrowing strategies from Ebola, dengue and malaria for alternative ways to stop the disease.

TRANSLATION IN BRIEF

AIMING HIGH

A Japanese study suggests activating phagocytosis by AIM could provide a path for acute kidney injury that doesn't lead to renal fibrosis.

RETRO ACTIVE

A group from Paul-Ehrlich-Institut has found a problem, and ways to solve it, with transposable elements in iPS cells.

DISTILLERY

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Sharfstein also challenged the idea that drug companies possess data that are important to clinicians that are not available from other sources.

CHECKING COMPANY COMMUNICATIONS

Richard Schilsky, CMO of the American Society of Clinical Oncology, countered this assertion with the example of immune checkpoint inhibitors. He noted that FDA has approved three checkpoint inhibitors for three different diseases — melanoma, lung cancer and kidney cancer — “but there is a list as long as your arm of tumor types where these drugs clearly have efficacy.”

The evidence hasn't been established in ways that meet FDA's standards for labeling, but “every oncologist” and “every patient” knows the data are coming, he said. Schilsky was a member of the working group that wrote the white paper.

Manufacturers have a great deal of data about checkpoint inhibitors “that is not in the labels that doctors would benefit from hearing about in an organized way, and that patients would benefit from hearing about in an organized way,” Schilsky said. “Those sponsors can't communicate it, and it just seems to me that we have to work towards a mechanism by which those sorts of communications can go forward.”

FDA's restrictions on labeling and communications are a disincentive for companies to conduct research that could benefit patients, Michael Listgarten, associate general counsel at the [Genentech Inc.](#) unit of [Roche](#), said at the Duke-Margolis Center meeting.

Listgarten said researchers at Genentech often propose studies and management asks whether the company would be able to communicate the data in a meaningful way. “Unless you can run two adequate, well-controlled clinical studies, you may not be able to put it in the label, and you may not be able to speak to it under FDA's current interpretation of their regulations. A lot of times we just put that study aside,” he said. [bc](#)

COMPANIES AND INSTITUTIONS MENTIONED

[Amarin Corp. plc](#) (NASDAQ:AMRN), Dublin, Ireland

[American Society of Clinical Oncology](#) (ASCO), Alexandria, Va.

[Center for Medicine in the Public Interest](#), New York, N.Y.

[Duke-Margolis Center for Health Policy](#), Durham, N.C.

[Genentech Inc.](#), South San Francisco, Calif.

[Johns Hopkins Bloomberg School of Public Health](#), Baltimore, Md.

[Pharmaceutical Research and Manufacturers of America](#) (PhRMA), Washington, D.C.

[Roche](#) (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland

[U.S. Centers for Medicare and Medicaid Services](#) (CMS), Baltimore, Md.

[U.S. Food and Drug Administration](#), Silver Spring, Md.

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[Usdin, S.](#) “Freeing speech.” *BioCentury* (2015)

REGULATION

COMPETITIVE CONSEQUENCES

BY STEPHEN HANSEN, ASSOCIATE EDITOR

Whatever the reason FDA refused to file an NDA for [Catalyst Pharmaceuticals Inc.](#)'s Firdapse amifampridine, the delay could allow a competitor with a less expensive form of the molecule to gain ground in a race to market.

Since Firdapse and 3,4-diaminopyridine (3,4-DAP) from Jacobus Pharmaceutical Co. Inc. have the same active ingredient, and both have Orphan Drug designation to treat Lambert-Eaton myasthenic syndrome (LEMS), only the first one approved will be allowed on the market for seven years.

LEMS is a rare autoimmune disease in which autoantibodies attack voltage-gated calcium channels, reducing the amount of acetylcholine released from nerve terminals. The primary symptom of the disease is severe muscle weakness, which can be life-threatening if the weakness involves respiratory muscles.

3,4-DAP is a potassium channel blocker that has never been approved in the U.S. but has been used to treat LEMS since the early 1980s. Firdapse is a phosphate salt of 3,4-DAP, which Catalyst claims to be more stable than the base formulation.

In the U.S., 3,4-DAP has been available through compounding pharmacies and for free through an expanded access program Jacobus has been running for 20 years.

Catalyst acquired North American rights to Firdapse from [BioMarin Pharmaceutical Inc.](#) in 2012. At the time, Firdapse was in an ongoing Phase III trial in LEMS that BioMarin had started in June 2011.

FDA granted the product breakthrough therapy designation in 2013, and in October 2014 Catalyst announced Firdapse had met the co-primary endpoints in the 38-patient Phase III trial, showing a significant improvement in Quantitative Myasthenia Gravis (QMG) and Subject Global Impression (SGI) scores from baseline to day 14 vs. placebo.

In December, Catalyst completed a rolling NDA submission for Firdapse to treat LEMS and congenital myasthenic syndromes (CMSs). The company requested Priority Review.

Catalyst declined BioCentury's interview request and did not disclose FDA's reasons for refusing to file the NDA, except to say in a statement on Feb. 17 that FDA found the application "was not sufficiently complete, and requests additional supporting information."

In January 2014, Catalyst said that at a Type B breakthrough therapy meeting with FDA, the company provided a briefing package that included data from 54 preclinical studies, six clinical trials and manufacturing information.

The company has not disclosed the data that supported breakthrough designation, or said how many randomized, controlled trials were included in the NDA.

If the Phase III study was the only one, it is possible that FDA wants another. According to a policy document from the Center for Drug Evaluation and Research, staff will refuse to file an application that relies on a single adequate and well-controlled study if prior communication with the sponsor indicated two would be needed, and if the company fails to justify the reason for submitting only one.

Catalyst expects to have data from a second trial in April. The study, which began in October, is a randomized, double-blind and placebo-controlled Phase III trial in 10 pediatric CMS patients. The company said at the time that the design was based on FDA guidance from a pre-NDA meeting in January 2015.

“WE HAVE BECOME INCREASINGLY CONCERNED THAT, IF GRANTED AN EXCLUSIVE U.S. MARKETING LICENSE FOR 3,4-DAP, THE CATALYST PRICE OF FIRDAPSE WILL BE EQUAL TO OR GREATER THAN ITS PRICE IN EUROPE.”

PHYSICIAN EDITORIAL, *MUSCLE & NERVE*

Of course, it is also possible that some other section or sections of the NDA were not complete.

PRE-PRICING PRESSURE

One thing that is certain is that the political climate around drug pricing has shifted dramatically since 2013 when FDA granted breakthrough therapy designation for Firdapse, and a large group of U.S. doctors has expressed concern that Catalyst would price the drug so high as to be out of reach.

A group of 106 neurologists who treat LEMS signed an editorial published this month in *Muscle & Nerve* that stated both the Catalyst and Jacobus products were safe and effective. However, the neurologists said, "we have become increasingly concerned that, if granted an exclusive U.S. marketing license for 3,4-DAP, the Catalyst price of Firdapse will be equal to or greater than its price in Europe."

BioMarin markets Firdapse to treat LEMS in Europe. According to a 2010 policy document published by NHS East Midlands Specialised

Commissioning Group, BioMarin's price for Firdapse was about £44,000 (\$62,300) per patient per year, compared with £1,200 (\$1,700) for 3,4-DAP from compounding pharmacies.

The East Midlands group decided to make the base form available to patients, and declined to fund Firdapse.

Catalyst began to make Firdapse available for free under an expanded access program in 2014. But the company has provided hints at an annual price for the drug of \$37,500-\$112,500 if it gets approved.

Specifically, in December, a company presentation pegged the U.S. market opportunity for Firdapse at \$300-\$900 million, with an estimated 8,000 patients eligible for treatment. That includes 3,000 LEMS patients and up to 1,500 CMS patients, plus a future indication in myasthenia gravis-MuSK antibody patients.

The neurologists seem to think Jacobus would be more responsible in setting its price than Catalyst.

"Catalyst is a publicly traded company, with a fiduciary obligation to optimize stockholder share price. Jacobus is a family-owned corporation that has been providing 3,4-DAP for free for two decades to patients followed by individual IND holders in the U.S.," they noted.

The doctors asked FDA to consider approving both drugs in the U.S.

Jacobus also declined to discuss its development and regulatory plans for 3,4-DAP, or potential pricing.


According to ClinicalTrials.gov, the company only began a clinical trial of 3,4-DAP in January 2012, six months after BioMarin started its Phase III study.

Last year Jacobus presented data from the randomized, placebo-controlled Phase II DAPPER trial in 32 LEMS patients at the American Association of Neuromuscular & Electrodiagnostic Medicine annual meeting. The withdrawal-design study met the primary endpoint: none

of the 14 patients receiving 3,4-DAP had a 30% deterioration in the triple timed up and go test (3TUG) after 3.5 days, whereas 13 of 18 patients tapered to placebo did ($p < 0.0001$).

The study also showed statistical significance on the secondary endpoints of self-assessment of LEMS-related weakness ($p = 0.0007$) and change in compound muscle action potential (CMAP) amplitude (no p-value given).

In investor presentations, Catalyst contends its commercial strategy won't inhibit patient access to 3,4-DAP. In a presentation this month, Catalyst said it would aim to minimize out-of-pocket costs and would offer patient support services including reimbursement assistance and financial assistance for eligible patients.

In the statement announcing the refusal-to-file letter, Catalyst said it expects to work with FDA "over the coming weeks in an effort to resolve the open issues and to define a path forward for a successful resubmission of our application at the earliest point in time." 

COMPANIES AND INSTITUTIONS MENTIONED

American Association of Neuromuscular & Electrodiagnostic Medicine, Rochester, Minn.
 BioMarin Pharmaceutical Inc. (NASDAQ:BMRN), San Rafael, Calif.
 Catalyst Pharmaceuticals Inc. (NASDAQ:CPRX), Coral Gables, Fla.
 Jacobus Pharmaceutical Co. Inc., Princeton, N.J.
 U.S. Food and Drug Administration (FDA), Silver Spring, Md.

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EBB & FLOW

FULL-SPECTRUM INVESTING

New investment firm [Perceptive Bioscience Investments Ltd.](#) is hoping its evergreen structure will give it the flexibility to find attractive valuations anywhere from seed-stage company formation to public equity.

On Feb. 22, Perceptive launched with undisclosed funding from Woodford Investment Management and other institutional investors. The London-based firm, which also has offices in New York, is led by CEO Joe Anderson, who was previously a partner at Abingworth.

Anderson told BioCentury Perceptive will invest across the life sciences space from therapeutics to medtech and from company formation and academic spinouts through to commercial public companies.

“We’re not going to have any allocation between public and private, or between early and late stage,” Anderson said. “What we’re focused on primarily is the quality of the underlying asset, whatever the technology happens to be.”

He noted Perceptive’s evergreen fund structure allows the firm to find the best valuations regardless of public market conditions.

Anderson said that in hot markets, early stage valuations aren’t connected to how well the public markets are performing. “The spinout from the university doesn’t really care too much about the level of the NASDAQ biotech index,” he said. On the flip side, in weak markets, he said many companies can be significantly down from their 52-week highs and in need of recapitalization — an area Anderson specialized in while at Abingworth.

“A lot of these companies through no fault of their own are going to have valuations which are depressed and have nothing to do with the intrinsic value of the asset,” he said. “It is a setting where we are seeing quite a lot of value at the moment.”

Anderson added that Perceptive will be able to support portfolio companies longer with the evergreen structure. He said traditional VC funds are sometimes “forced to get an exit in a company that is going well, which can be unfortunate for returns. So with this structure we are able to stay the course.”

Anderson is joined by Jonathan Peacock as chairman and serial biotech entrepreneur Sir Chris Evans as deputy chairman. Peacock was formerly CFO at [Amgen Inc.](#) (NASDAQ:AMGN) and [Novartis AG](#) (NYSE:NVS; SIX:NOVN). Evans is also chairman of Arthurian Life Sciences, which manages the Welsh Life Sciences Fund ([see BioCentury, Feb. 4, 2013](#)).

— *Stephen Hansen*

SINGAPORE SWING

Armed with its \$50 million Lightstone Singapore L.P. fund, Lightstone Ventures is making its first foray into Asia with plans to capitalize on Singapore’s ripening life sciences ecosystem.

Lightstone launched the fund on Feb. 17 with investors including Limited Partners Temasek and the EDBI corporate investment arm of the Singapore Economic Development Board.

Lightstone’s Mike Carusi noted that the Singapore government has made a significant effort to invest in the life sciences over the past 15 years.

“In the early years, it was about basic research and building up infrastructure, and then there was more of a focus on translating research into commercial enterprises. As that early investment matures, we’re looking to now capitalize on that and be a catalyst for company formation,” said Carusi, who added that only a handful of VCs are tapping into Singapore’s early stage life sciences.

“WHAT WE’RE FOCUSED ON PRIMARILY IS THE QUALITY OF THE UNDERLYING ASSET, WHATEVER THE TECHNOLOGY HAPPENS TO BE.”

JOE ANDERSON, PERCEPTIVE BIOSCIENCE

“WE WANT DRUG DISCOVERY ENGINES.”

MIKE CARUSI, LIGHTSTONE VENTURES

Lightstone plans to create four to five newcos in the next three to four years around technologies emerging from universities, hospitals and government research institutes including Singapore's [Agency for Science, Technology and Research \(A*STAR\)](#).

The companies may span therapeutics, medical devices, diagnostics and research tools.

Within therapeutics, Carusi said, "We want drug discovery engines. That's been our strategy in the U.S. and that is our strategy within Singapore. We tend not to invest in single-asset companies. We like to have some underlying platform with the ability to generate multiple shots on goal that we can then partner around."

The firm plans to allocate \$10-\$15 million to each newco and is aiming for an 8-10x return on investment within six to eight years. Carusi expects the first company to launch within the next 12 months.

Lightstone may also pursue one or two opportunistic investments in established companies in Singapore that can bring a 3-5x return on a two-to four-year timeline.

Lightstone was formed in 2012 by the general partners and other members of life sciences teams of venture firms [ATV](#) and [Morgenthaler Ventures](#). Lightstone's first fund closed in 2014 with \$172 million.

"It's no longer strictly a U.S.-based game. We need to have a presence and partners in Europe and Asia to allow us to expand our portfolio and explore different strategic relationships, different capital sources and different approaches towards commercialization," said Carusi.

— Virginia Li

LIGHTSPEED'S MAGIC NUMBER

[Forty Seven Inc.](#)'s combination of novel mechanism, advanced stage of development and management team convinced Lightspeed Venture Partners to make its first-ever therapeutics investment.

On Feb. 24, the newco raised \$75 million in a series A round co-led by Lightspeed and [Sutter Hill Ventures](#), with participation from [Clarus Ventures](#) and [GV \(formerly Google Ventures\)](#). Alongside the financing, Forty Seven received exclusive, worldwide rights from [Stanford University](#) to a pipeline of immuno-oncology molecules.

The lead program is Hu5F9-G4, a mAb against CD47 that is in two Phase I trials to treat solid tumors and acute myelogenous leukemia (AML), with data expected this year.

Forty Seven CEO Jonathan MacQuitty said inhibiting CD47 engages the innate immune response by preventing cancer cells from evading phagocytosis via macrophages. He added that inhibiting CD47 can also prime an antitumor T cell response, providing potential synergies with checkpoint inhibition.

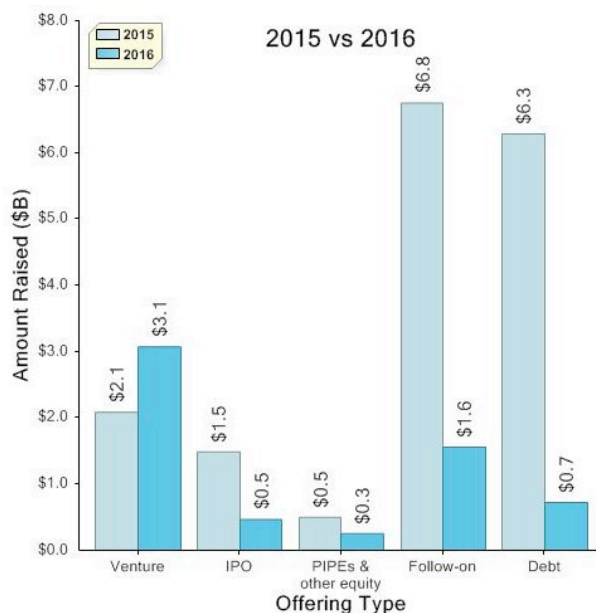
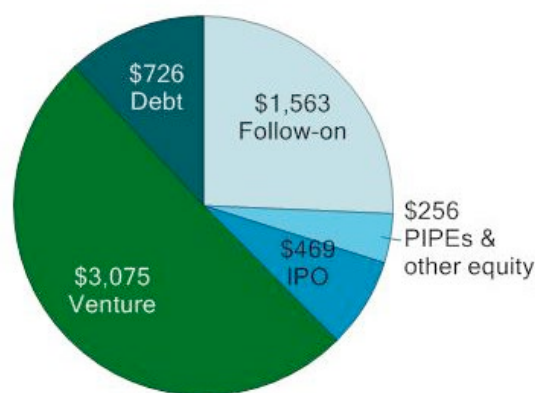
Lightspeed invests primarily in tech, Internet and consumer companies but has made five other biotech investments, including cancer diagnostics play [Guardant Health Inc.](#) and genomics company [Personalis Inc.](#)

"Biotech is not a mainstream part of our investment program; it is really just done on an opportunistic basis," Lightspeed's Chris Schaepe told BioCentury.

MONEY RAISED IN 2016

Last week, the biotech industry raised \$392 million, bringing to \$6.1 billion the total raised year-to-date. In 2015, a total of \$110.3 billion was raised, including \$56.6 billion in debt, \$29.7 billion in follow-ons, \$3.7 billion in PIPEs and other equity, \$8.1 billion in IPOs, and \$12.2 billion in venture capital. Totals include overallocments and warrants, and are rounded to the nearest millions.

Total YTD: \$6,087 (\$M)



He said three factors led to Lightspeed making its first therapeutics investment: Hu5F9-G4's potential for broad applicability across various cancers; its late stage of development for a series A round; and the experienced management team. MacQuitty is also chairman of Personalis and was previously a partner at Abingworth.

"We made an exception. This really was a unique opportunity," Schaepe said.

MacQuitty said the cash should give Forty Seven at least three years of runway and will enable the company to complete the current monotherapy

trials and future combination studies. The company expects to start two combination trials of Hu5F9-G4 this year and two more in 2017.

He said the company has had discussions with pharma companies about collaborating on combinations trials. In addition, Forty Seven has a preclinical pipeline of undisclosed checkpoint inhibitors and other cancer mAbs that could be tested in combination with Hu5F9-G4. [ba](#)

— *Stephen Hansen*

EARNINGS ON DECK

At least three biotechs and pharmas are expected to report earnings this week. (A) FY14 core EPS

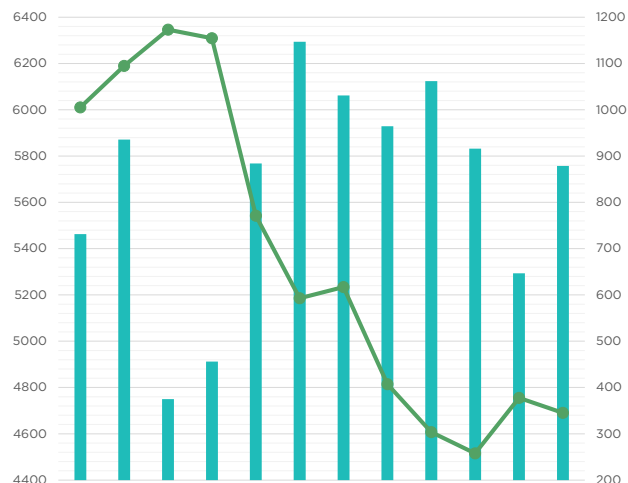
Company	Date	Pre/post mkt	4Q15 EPS est	4Q14 EPS	Expected chg
Endo International plc (NASDAQ:ENDP; TSX:ENL)	2/29	Pre	\$1.27	\$1.16	9%
Arena Pharmaceuticals Inc. (NASDAQ:ARNA)	2/29	Post	-\$0.13	-\$0.15	NA
Ipsen Group (Euronext:IPN; Pink:IPSEY)	3/1	NA	NA	€2.22 (A)	NA

Analyst picks & changes

Company	Bank	Analyst	Coverage	Opinion	Wk chg	2/26 cls
Achillion Pharmaceuticals Inc. (NASDAQ:ACHN)	Baird	Brian Skorney	Upgrade	Outperform (from neutral)	10%	\$7.35
Skorney upgraded and maintained his \$10 target ahead of HCV data from a Phase IIa trial of Achillion's odalasvir plus simeprevir and AL-335 from Johnson & Johnson (NYSE:JNJ). He believes "the stock can see significant upside if the six-week duration is able to achieve 100% SVR [sustained virologic response]." J&J has exclusive, worldwide rights to develop and commercialize HCV products and regimens containing one or more HCV assets from Achillion, including odalasvir, a pan-genotypic, second-generation HCV NS5A protein inhibitor. J&J markets Olysio simeprevir, an HCV NS3/4A protease inhibitor; it has ex-Nordic rights to the drug from Medivir AB (SSE:MVIR B). AL-335 is a uridine-based nucleotide analog inhibitor of HCV NS5B polymerase.						
Keryx Biopharmaceuticals Inc. (NASDAQ:KERY)	JPMorgan	Whitney Ijem	Downgrade	Neutral (from overweight)	0%	\$3.64
Ijem downgraded and withdrew her \$11 target, saying she is "increasingly less confident in outer year growth" of anemia drug Aurixia ferric citrate. She cites a lack of "meaningful acceleration in scripts in the last several months" and "unclear timelines to increased reimbursement coverage." The drug was launched in December 2014 and had U.S. revenues of \$10.1M in 2015. Ijem lowered her peak U.S. sales estimate for the product to about \$500M from about \$700M. Aurixia is partnered with Panion & BF Biotech Inc. (Taiwan:1760).						
Orexigen Therapeutics Inc. (NASDAQ:OREX)	Leerink Partners	Paul Matteis	Downgrade	Market perform (from outperform)	-42%	\$0.97
Matteis also lowered his target to \$2 from \$4.50 on "little growth" in prescriptions of Orexigen's obesity drug Contrave naltrexone/bupropion over the past seven months. He noted that the average weekly prescription growth rate from July 3, 2015 to Feb. 5, 2016 was 0.4%. He also spoke with multiple payers who expressed a cautious near- to mid-term outlook for reimbursement in the obesity market.						
PTC Therapeutics Inc. (NASDAQ:PTCT)	Jefferies	Gena Wang	Upgrade	Hold (from underperform)	-72%	\$7.99
	RBC Capital Markets	Simos Simeonidis	Downgrade	Sector performer (from outperform)		
Wang upgraded following the decline in share price on the FDA refusal-to-file letter concerning PTC's NDA for Translarna ataluren to treat nonsense mutation Duchenne muscular dystrophy (DMD). She thinks the news is now priced in the valuation. Wang lowered her target to \$12 from \$18 after reducing Translarna's probability of success to 5% from 20% for DMD in the U.S. and cystic fibrosis (CF) in the U.S. and EU and to 30% from 50% for DMD in the EU and the rest of the world. By year end, PTC expects to report data from a Phase III trial of the small molecule that facilitates complete translation of proteins containing nonsense mutations to treat CF.						
Simeonidis also lowered his target to \$11 from \$56 on the refusal-to-file letter. He removed all U.S. DMD revenue from his model.						
Radius Health Inc. (NASDAQ:RDUS)	Jefferies	Eun Yang	Downgrade	Hold (from buy)	11%	\$30.00
Yang downgraded after shares rose following Phase III osteoporosis data from competitor compound romosozumab that was "not as strong" as data seen with Radius' abaloparatide-SC. She now views meaningful upside as unlikely, with abaloparatide-SC approvability largely priced in. The subcutaneous peptide analog of parathyroid hormone-related protein (PTHrP) is under EMA review with an NDA submission slated for this quarter. Radius has exclusive, ex-Japanese rights to the compound from Ipsen Group (Euronext:IPN; Pink:IPSEY). Romosozumab is a humanized mAb against sclerostin from Amgen Inc. (NASDAQ:AMGN) and UCB Group (Euronext:UCB).						

BIOCENTURY 100 PRICE & VOLUME TREND

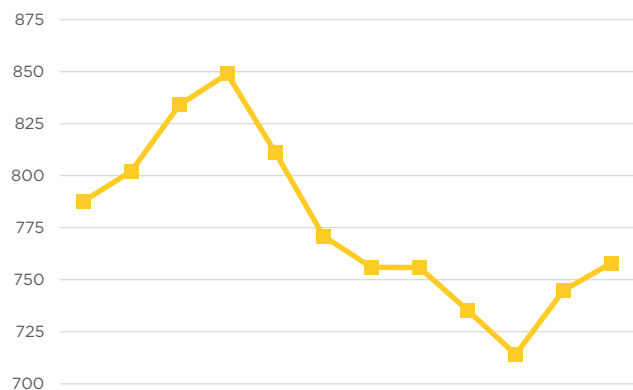
Cumulative weekly performance of 100 bioscience stocks. 12-week period. Line shows Price Level change (Left scale. Index base=1000 on May 10, 1996). Bars show cumulative volume in millions (right scale).



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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 2/26/16



PRICES
4690.76
dn 1%

VOLUME
878.8M shrs
up 36%

PRICE GAINS

Stocks with greatest % price increase in the week ended 2/26. (Priced above \$2; 5,000 minimum share volume)

Company	Ticker	\$Close	\$Chg	% Chg	Vol(00)
Editas Medicine	EDIT	27.490	9.010	49%	22360
NanoViricides	NNVC	2.500	0.740	42%	28029
Parnell Pharmaceuticals	PARN	2.870	0.740	35%	10148
Ziopharm Oncology	ZIOP	7.840	1.690	27%	161649
Pulmatrix	PULM	2.727	0.584	27%	807
SanBio	4592	¥970.000	¥198.000	26%	5185
CytoSorbents	CTSO	5.120	1.030	25%	7074
Xtant Medical	XTNT	3.227	0.627	24%	469
Aclaris	ACRS	18.930	3.640	24%	3246
Trovagene	TROV	5.360	1.010	23%	34011

PRICE DECLINES

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

Company	Ticker	\$Close	\$Chg	% Chg	Vol(00)
PTC	PTCT	7.990	-20.850	-72%	481543
Chimerix	CMRX	4.720	-2.910	-38%	347341
Cara Therapeutics	CARA	4.760	-2.840	-37%	47119
OBI Pharma	4174	NT\$463.00	-NT\$218.00	-32%	218304
CombiMatrix	CBMX	4.228	-1.282	-23%	644
UMN Pharma	4585	¥1941.000	-¥559.000	-22%	27276
Relypsa	RLYP	14.600	-3.800	-21%	179981
OvaScience	OVAS	5.120	-1.270	-20%	18378
MDxHealth	MDXH	€2.910	-€0.710	-20%	12786
Forward Pharma ¹	FWP	12.830	-2.920	-19%	1938

VOLUME GAINS

Greatest changes in volume above 5,000 shares.

Company	Ticker	Vol(00)	%Chg	\$Close	\$Chg
Ocera	OCRX	8446	2779%	3.000	+0.120
Farona Pharmaceuticals	FARN	195	1946%	262.5p	-2.5p
PTC	PTCT	481543	1592%	7.990	-20.850
Intellipharmaceuticals ²	IPCI	15516	1471%	2.710	+0.370
Check-Cap	CHEK	550	1420%	3.300	+0.550
Parnell Pharmaceuticals	PARN	10148	827%	2.870	+0.740
Innocoll ³	INNL	3654	706%	8.730	+0.130
CellSeed	7776	8098	572%	¥619.000	+¥66.000
AxoGen Inc.	AXGN	4511	528%	5.290	+0.270
Trevena	TRVN	57362	466%	9.180	+1.120

1 Volume reflects ADS (IADS = 1 share)

2 Includes volume from Toronto Stock Exchange (TSX)

3 Volume reflects ADS (IADS = 13.25 shares)

BIOCENTURY 100 ADVANCE-DECLINE TRENDS

Week ended	BC100 Price Level	BC100 Stocks gaining	Gaining vol. (00)	BC100 Stocks declining	Declining vol. (00)
Jan 29	4814.53	12	1478634	88	8169226
Feb 05	4607.46	22	3471176	78	7147133
Feb 12	4515.59	32	3489975	67	5582928
Feb 19	4755.23	88	5041659	11	1407236
Feb 26	4690.76	43	3745914	56	4972708

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