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

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.

with checkpoint agents, and already a few pharmas 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.
“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 cancer 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.

Ammgen 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.

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“We think PD-1 antibodies are the ready-made solution — they’re made to go together,” said Virtu 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 DXN-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. DXN-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 cossackievirus 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.

Oncolyx 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 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.

Virту 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 Virțu 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 DXN-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.

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: BIOIQ: BioCentury Online Intelligence
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, adenoaviral 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
“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, Imlytic 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, Oncolyt BioPharma Inc. and Oryx GmbH & Co. KG, are investigating co-administering the therapies with HDAC inhibitors. Oncolyts President and CEO Yasuo Urata said HDAC inhibitors increase tumor cells’ ability to uptake Telomelynin (OBP-301) via the coxsackie adenovirus receptor (CAR).

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

Similarly, Genelix Corp. is using Roche and Genentech Inc.’s Avastin bevacizumab to increase tumor uptake of GL-ONC1 (GLV-1h68).

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

GL-ONC1 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 Genelix 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.

Oncolyt is doing both: it is developing a version of its therapeutic oncolytic virus Telomelynin 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.

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In November 2015 Oncolyt granted Liquid Biotech USA Inc.’s 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

- 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.
- Mayo Clinic, Rochester, Minn.
- Medimmune LLC, Gaithersburg, Md.
- Merck & Co. Inc. (NYSE:MRK), Kenilworth, N.J.
- Omnis Pharma Inc., Rochester, Minn.
- Oncolyx 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. (ASK:VLA; OTCQX:VRACY), Pymble, Australia
- Virtu Biologics Ltd., Glasgow, U.K.

REFERENCES