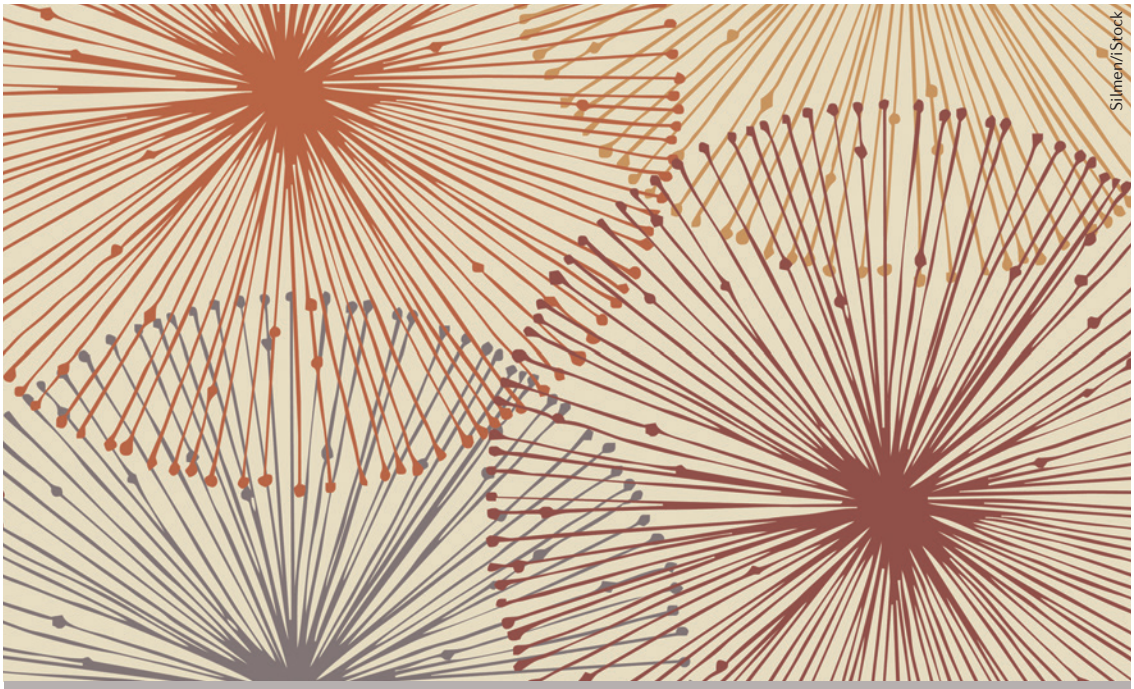


# Oncolytic viruses get a boost with first FDA-approval recommendation

The future of cancer-killing viruses lies in their potential to augment cell and antibody immunotherapies.

*Elie Dolgin*

A virus engineered to infect and destroy tumour cells stands on the cusp of regulatory approval by the US Food and Drug Administration (FDA). On 29 April, members of an expanded advisory committee to the agency voted 22 to 1 in favour of allowing sales of talimogene laherparepvec (T-VEC) — a version of the herpes simplex virus that both attacks cancer cells and enhances antitumour immune responses — for the treatment of unresectable and recurrent melanoma.

If approved, T-VEC will become the first tumour-targeted viral agent to reach pharmaceutical shelves outside of China. Such a stamp of approval could usher in a long-awaited era of viral therapies for cancer and provide a powerful tool for enhancing the efficacy of the latest immune-stimulating antibodies and cell therapies. "It's an exciting time for our patients," says Howard Kaufman, Chief Surgical Officer at the Rutgers Cancer Institute of New Jersey, New Brunswick, New Jersey, USA, who led the T-VEC trials. "This will open up a completely new class of drugs."

The FDA will make a full licensing decision by 27 October. An evaluation for European marketing authorization is expected before the end of the year.

T-VEC is being developed by the biotech giant Amgen, which in 2011 promised to pay up to US$1 billion (including $575 million in milestone commitments) to acquire the product's inventor, BioVex Group. In the therapy's Phase III trial, 16% of the 295 participants who received intralesional doses of T-VEC experienced a durable response — their tumours shrank for at least 6 months — whereas only 2% of the 141 participants who received subcutaneous shots of granulocyte–macrophage colony-stimulating factor (GM-CSF) showed such a response.

Although patients who took T-VEC gained an average of just 4.4 months of life over those who took GM-CSF — with median survival times of 23.3 months and 18.9 months, respectively — 11% of T-VEC recipients showed no signs of cancer after treatment. This complete response rate

surpasses even those seen in trials for all recently approved immunotherapy drugs approved for melanoma, although the study population included more patients with earlier-stage disease, clouding direct comparisons.

### Go together

Many researchers expect to see even better response rates when T-VEC is combined with checkpoint-blocking antibodies — and trials are ongoing to test two-hit regimens. Drug developers are pairing T-VEC with Bristol-Myers Squibb's ipilimumab, a cytotoxic T-lymphocyte protein 4 (CTLA4)-specific antibody, in a Phase Ib/II study.

The preliminary data "suggest that there is in fact a significant added benefit of the combination," says Kaufman, one of the trial investigators who reported early findings from this study at this year's meeting of the American Society for Clinical Oncology. Plus, "almost all of the side effects we see are related to the ipilimumab," notes surgical oncologist Robert Andtbacka, another investigator from the University of Utah's Huntsman Cancer Institute, in Salt Lake City, Utah, USA. "We don't seem to have a substantial increase in toxicity, which is reassuring." Late last year, Kaufman, Andtbacka and their colleagues also began enrolling melanoma patients to receive Merck & Co.'s programmed cell death protein 1 (PD1)-specific antibody pembrolizumab with or without T-VEC.

Based on the preliminary combination data, "I think clinicians are going to make that leap of faith" — and prescribe both therapies together — "if the insurance companies let us," says Sanjiv Agarwala, Chief of Medical Oncology and Hematology at St. Luke's Cancer Center in Bethlehem, Pennsylvania, USA, who is involved in the pembrolizumab trial. "It's a matter of what's going to be reimbursed."

John Bell, a senior scientist at the Ottawa Hospital Research Institute in Ontario, Canada, who directs the Canadian Oncolytic Virus Consortium, describes the coupling of cancer-attacking viruses with checkpoint blockade as "a match made in heaven". Although researchers originally thought of these viruses as killing machines that would replicate inside cancer cells and induce cell lysis — hence the name 'oncolytic' virotherapy — many viral products act more like cancer vaccines.

"It's incredibly exciting that we now recognize that [oncolytic viruses] stimulate antitumour immunity," Bell says, "and what great timing that we actually have things to take the brakes off the antitumour immune response as well".

Some investigators are also beginning to combine oncolytic virotherapy with adoptive T-cell therapies. Last year, for example, a research team from the Baylor College of Medicine in Houston, Texas, USA, reported that an armed oncolytic adenovirus boosted the efficacy of a chimeric antigen receptor (CAR) immunotherapy in mouse models of neuroblastoma (*Cancer Res.* **74**, 5195–5205; 2014). The Finnish start-up TILT Biotherapeutics plans to launch a Phase I trial of this combination strategy for melanoma in 2016.

Big pharma is taking notice, and thinking beyond T-VEC. "They're reaching out to virus companies now to say, 'we'd like to work with you to do combination therapies'," says Frank Tufaro, Chief Executive of DNAtrix, which is developing the oncolytic adenovirus DNX-2401 for glioblastoma.

In January 2015, the AstraZeneca subsidiary MedImmune also announced a deal to test its portfolio of immunotherapeutic agents together with an engineered strain of vesicular stomatitis virus from Omnis Pharmaceuticals.

### An infectious approach

Oncolytic viruses are built to replicate in and rupture cancer cells — inducing the release of tumour antigens and generating anticancer immunity, while leaving normal cells alone. As such, they often need careful genetic engineering. In the case of T-VEC, this meant boosting the herpesvirus' ability to hone in on cancer cells, by deleting the viral gene encoding infected cell protein 34.5 (ICP34.5). By deleting ICP47, which blocks antigen presentation on infected cells, viral engineers aimed to induce a more potent immune response (the deletion of ICP47 also leads to earlier expression of the glycoprotein US11, which also enhances replication in cancer cells.)

T-VEC, like several other products in the oncolytic pipeline, also has an added element of immune stimulation deliberately built into the virus. Scientists generally include transgenes that encode a range of cytokines and chemokines in their viruses, to stimulate various lymphocyte populations and drive immune responses. The most widely used such cytokine is GM-CSF, which is incorporated into T-VEC and three other mid- to late-stage clinical candidates (TABLE 1).

While the majority of the oncolytic pipeline involves genetic engineering, some drug developers instead rely on the inherent tumour-destroying properties of some viruses. Viralytics' CVA21, for example, uses a proprietary formulation of a common-cold coxsackievirus to infect and enter cells through the intercellular adhesion molecule 1 (ICAM1) surface protein, which is overexpressed on many cancer cells.

Oncolytics Biotech similarly makes use of the natural properties of its RNA virus. The respiratory enteric orphan virus preferentially replicates in Ras-activated cells, which cannot mount a proper antiviral response, making cancer cells its preferred breeding ground. The company's unmodified proprietary formulation of the oncolytic virus, called pelareorep, is in mid-stage trials for lung, breast, colon, pancreas and other cancers, after having suffered a set-back in a Phase III trial in head and neck cancer.

"The differences between the viruses are bigger than people realize, and that just means we have more shots on net" to find something that works for each kind of cancer, says Bradley Thompson, Chief Executive Officer of Oncolytics. "We're all different, and I think we're all getting a sense now of where our agents work, where they don't work and why."

Table 1 | **Selected oncolytic viruses in development**

| Drug | Sponsor | Indication | Phase |
|---|---|---|---|
| Talimogene laherparepvec* | Amgen | Melanoma | BLA |
| CG0070* | Cold Genesys | Bladder cancer | II/III |
| Pexastimogene devacirepvec* | SillaJen Biotherapeutics | Liver cancer | II |
| CVA21 | Viralytics | Melanoma | II |
| Pelareorep‡ | Oncolytics Biotech | Various solid tumours | II |
| Enadenotucirev | PsiOxus Therapeutics | Various solid tumours | I/II |
| DNX-401 | DNAtrix | Glioblastoma | Ib |
| ONCOS-102* | Oncos Therapeutics | Various tumours | I |

*Granulocyte–macrophage colony-stimulating-factor-producing oncolytic virus. ‡RNA virus. BLA, biologics license application.

**Viral marketing**

Although sales of oncolytic virotherapies will probably be modest compared with those of other emerging oncology drug classes, these viruses could still be important money-makers. In a report released last year, Valerie Kellogg, a pharmaceutical analyst with BCC Research, estimated that the global market for oncolytic virotherapies will reach $6.4 billion by 2023.

Douglas Loe, a biotech analyst with Euro Pacific Canada, agrees that the "relatively minor side-effect profiles" of these products could make for a strong market potential.

The field's projected pay day has been a long time in the making. The idea of treating cancer with viruses dates back over a century to a 1912 report that a rabies vaccine that was administered to a woman after a dog bit her led to remission of a large cervical tumour. Physicians dabbled with viral therapy throughout the twentieth century, but it wasn't until the emergence of modern genetic engineering that the field really took off. In 1991, Robert Martuza and his colleagues at Harvard Medical School in Boston, Massachusetts, USA, described the first laboratory-modified virus for combatting brain tumours in mice (*Science* **252**, 854–856; 1991).

In the early days of engineered virotherapy, however, many researchers and companies took a cautious approach, which led to products such as ONYX-015 — "the original flagship of the whole field," as Bell describes it. Onyx Pharmaceuticals' ONYX-015 was a modified adenovirus that contained gene deletions that were designed to facilitate its replication in cells that were defective for the p53 pathway, but it also had weak proliferative ability. (Controversy over ONYX-015's mechanism of action and Pfizer's acquisition of Onyx's development partner, Warner–Lambert, led to the product's abandonment in 2003 ahead of a planned Phase III trial. However, Chinese regulators approved an almost identical product, H101, for the treatment of head and neck cancer in 2005; it sells barely above $3 million per year.)

These first-generation viruses were "so attenuated that they'd be safe but, at the same time, they were not effective," says Bell. "We had to re-invent ourselves by getting new virus platforms out there that had a little more 'oomph' to them and that would be therapeutically useful as well as safe."

Bell is watching the early-stage pipeline for better things to come. "There's still a bit of a hangover from the early days," he says, "but the ones that are coming up behind are the ones that are more potent".

Researchers will convene this month in Boston for the 9th International Conference on Oncolytic Virus Therapeutics. In previous years, after the high-profile disappointments of ONYX-015 and other products, "people were fairly sombre" at this annual conference, says meeting organizer Antonio Chiocca, Neurosurgeon-in-Chief at the Brigham and Women's Hospital in Boston, Massachusetts, USA. With T-VEC on the verge of regulatory approval, Chiocca expects this year's gathering to have "a much more positive outlook."