milestone

THE ORIGINS OF oncolytic viral therapy

BY YUNING WANG, PHD

Since their discovery in the 1890s, viruses have intrigued scientists as potential cancer-killing agents. Early observations and experiments once excited them, but technical limitations soon dampened their hope. It wasn't until recent breakthroughs in genetic engineering that researchers began to harness viruses' full potential as targeted cancer therapies, turning these risky pathogens into lifesaving remedies.

EARLY 1900s — Remission to infection

Around the turn of the 20th century, physicians noticed that patients with cancer who contracted natural viral infections occasionally experienced temporary remissions. One of the earliest documented cases, reported in 1904 by George Dock, a physician at the University of Michigan, was about a female patient with myelogenous leukemia (1). After a bout of what was assumed to be influenza, her previously enlarged liver and spleen shrank to nearly normal size, and her elevated leukocyte count dropped more than 70-fold. The remission lasted for several months before her death a year and a half later.

In another case in 1912, physician Nicola De Pace described significant tumor regression in patients with cervical cancer who received rabies vaccines containing an attenuated strain of the rabies virus (2). These reports sparked curiosity among scientists to understand how viruses might interact with cancer in laboratory experiments.

In 1922, microbiologists Constantin Levaditi and Stefan Nicolau at the Pasteur Institute were working on a new vaccine against smallpox using the vaccinia virus. When they inoculated the virus into epithelial tumors in mice and rats, they discovered that it exhibited a selective affinity for the tumors, proliferating more rapidly in cancerous tissues than in normal ones. Levaditi and Nicolau described the tumors as acting like "a sponge attracting viral replication" (3).

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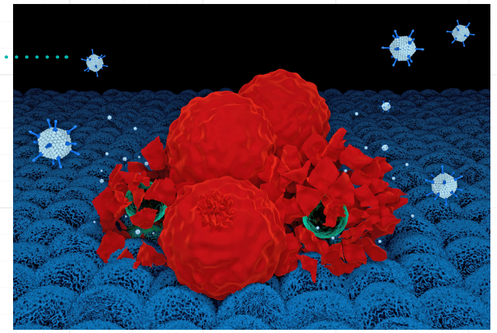
George Dock reported one of the earliest cases of tumor regression during natural viral infections, noting that such an unusual response might hold "something of therapeutic value" (1).



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Alice Moore, a researcher at Memorial Sloan Kettering Cancer Center, first demonstrated that viruses could kill tumor cells in living animals.

LATE 1940s–1950s — First insights into viral oncolysis

The early clinical observations of tumor regression induced by viral infections led to a wave of research in both laboratory and clinical settings between the late 1940s and 1950s. Alice Moore, a researcher at Memorial Sloan Kettering Cancer Center, implanted a transplantable mouse cancer, known as sarcoma 180, into a group of mice. She inoculated these mice with the Russian Far East encephalitis virus and monitored tumor growth and viral presence in the mouse tumors, brains, and blood.

In line with Levaditi and Nicolau's findings in 1922, Moore observed that the virus preferred tumor tissue over other tissues. Her microscopic examinations revealed that, in some cases, the virus completely destructed mouse sarcoma 180 tumors. When Moore transplanted these virus-infected tumors into healthy mice, the tumors failed to grow, suggesting that the virus had eradicated the cancer cells.

In 1949, Moore published her findings (4), demonstrating viral oncolysis in living animals for the first time. More studies on the oncolytic activity of other viruses using animal models followed. These studies laid the foundation for understanding the detailed mechanisms by which viruses selectively infect and kill cancer cells.

"In a normal cell, there is a whole set of antiviral machinery that recognizes viruses and signals the immune system to clear them quickly," explained Howard Kaufman, the president of Ankyra Therapeutics, a company that develops cytokine-based immunotherapies for cancer. "Cancer cells have defects in this antiviral machinery. That's why they're more susceptible to viruses."

During the 1950s, looser ethical guidelines for medical research allowed physicians to take bold approaches. They administered live viruses, such as hepatitis B virus, West Nile virus, and adenovirus, directly to patients with cancer (5–7). While some patients exhibited temporary tumor regression and symptom relief, others had no improvement or even severe, fatal viral infections. It became clear that viruses with greater tumor specificity and safer profiles were needed. Without the tools to precisely control and manipulate these viral properties, many researchers abandoned the field, until breakthroughs in genetic engineering emerged decades later.

1990s — Engineering a better virus

In the 1990s, molecular cloning techniques became standard for generating recombinant DNA, allowing researchers to insert and delete genes within an organism's genome. This brought about a resurgence of interest in oncolytic viruses.

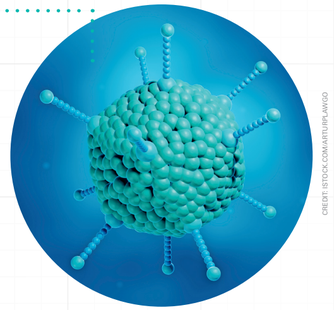
In 1994, David Kirn, now CEO and cofounder of 4D Molecular Therapeutics, completed his fellowship in medical oncology at the University of California, San Francisco, and was looking for a research project. With an interest in virology, Kirn interviewed with Onyx Pharmaceuticals, a newly founded company developing novel cancer therapies.

"They said there was this idea of using viruses against cancer," Kirn remembered. "I'd always been torn between my love of virology, infectious disease, and oncology. So, for me, it was the perfect fit."

Kirn became Onyx Pharmaceuticals' tenth employee and started working on creating new viruses that could selectively target cancer cells. "There were no engineered viruses that had been in the clinic before," Kirn said. The only related research he found was by Robert Martuza, a neurosurgeon at Massachusetts General Hospital, who had genetically modified a herpes simplex virus by deleting the thymidine kinase gene in 1991. With this modification, the virus replicated only in rapidly dividing tumor cells and inhibited tumor growth in mice (8).

Inspired by Martuza's study, Kirn worked with adenovirus, deleting its E1B gene to create a modified virus named ONYX-015. The E1B gene encodes a protein that binds to and inactivates the tumor suppressor p53 protein, preventing p53-mediated apoptosis and allowing viral replication in infected cells. Without the E1B gene, the ONYX-015 virus cannot inactivate p53 and cannot replicate in normal cells. However, it can replicate efficiently in p53-deficient tumor cells.

In 1997, Kirn and his team published results showing ONYX-015's remarkable antitumor effects in mice with a substantial reduction in tumor size and complete regression in 60 percent of the tumors (9). While presenting these encouraging results, Kirn and his team were also getting ready to test ONYX-015 in human trials.



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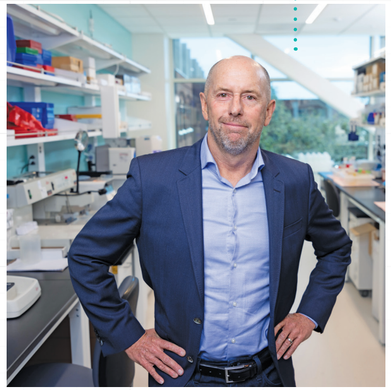
Using genetic engineering, David Kirn and his team at Onyx Pharmaceuticals created ONYX-015, a genetically modified adenovirus that selectively targets cancer cells.



CREDIT: DAVID KIRN

David Kirn led the clinical trials of the first engineered oncolytic virus, ONYX-015.

1996–EARLY 2000s — Navigating clinical challenges

Beginning in 1996, Kirn and the Onyx Pharmaceuticals team partnered with researchers from multiple institutions to carry out clinical trials for ONYX-015. "There were a lot of questions about how to use a therapeutic that amplifies in the human body," Kirn said. "There were also questions about how best to deliver the viruses."

To address these challenges, Kirn designed and implemented a novel clinical research and development approach. They began by injecting the treatment directly into patients' tumors to assess safety. Once proven safe, they progressed to injections into body cavities, arteries, and finally veins. The studies started with patients with advanced, incurable cancers and then included those with premalignant conditions (10).

"We treated over 400 patients with ONYX-015, exploring different tumor types and all routes of administration from intratumoral to intraperitoneal and intravenous," Kirn said. "As a physician, I was allowed to inject the first patient ever treated with an engineered oncolytic virus. The patient did quite well. That was incredibly exciting."

In one of the phase II trials, 37 patients with head and neck cancer received intratumoral injections of ONYX-015 in conjunction with two chemotherapy agents. The results exceeded those observed with chemotherapy alone, with 63 percent of patients experiencing significant tumor shrinkage and 27 percent achieving complete tumor regression (11). "We thought it could be dangerous. But we found the opposite. It was very, very safe," Kirn said. "We didn't see significant toxicities. Patients got a little bit of a flu-like syndrome. That was it."

However, ONYX-015 showed limited efficacy as a single agent. It failed to induce tumor regression in patients with deeply seated pancreatic, colorectal, and ovarian tumors (10). Consequently, further development of ONYX-015 was halted in the early 2000s. "I think the rest of the history of the field has been based on that ONYX-015 data," Krin said. "That's when people started trying new viral species that might be more potent and arming them with transgene payloads."

2015 — The first FDA approval

As the ONYX-015 program led by Krin concluded, Kaufman worked as a physician scientist at Columbia University Medical Center. There, he created a recombinant vaccinia virus expressing a tumor antigen to treat metastatic melanoma and demonstrated its potential clinical benefits in a phase I trial (12).

Kaufman's work caught the attention of Robert Coffin, a virologist who had recently founded a biotechnology company called BioVex. "Rob Coffin found my poster at a science meeting and said, 'We have an oncolytic herpes virus, and it looks like you're interested in this. Would you want to work with us?'" Kaufman recalled. "That was my introduction to T-VEC."

Talimogene laherparepvec (T-VEC) was a new oncolytic virus Coffin was developing. As a genetically modified herpes simplex virus, T-VEC had two key genes removed via recombinant DNA technology to prevent it from replicating in healthy cells and evading the host immune response. Additionally, Coffin engineered the virus to express granulocyte-macrophage colony-stimulating factor (GM-CSF).

"GM-CSF was known to recruit dendritic cells and help them to mature," Kaufman said. "To get a systemic immune response, a very strong T cell response is needed." Coffin anticipated that by expressing GM-CSF, which prompts dendritic cells to present tumor antigens to T cells, T-VEC would trigger an immune response against cancer cells.

Kaufman led the phase II trial of using T-VEC to treat melanoma intratumorally and published the results in 2009, which showed a 26 precent overall response rate (13). "A 20 or 30 percent response rate for melanoma at that time was really good. The only available therapy worked about 10 to 15 percent of the time," Kaufman said. Encouraged by these results, Kaufman went on to design and lead a randomized phase III study. This larger trial involved over 400 patients and yielded a similar response rate (14).

In 2015, after years of testing and trialing, the FDA approved T-VEC as the first oncolytic viral therapy. This new treatment option has since led to increased survival rates for patients with melanoma. "I remember telling one of my first patients who was going into the study, 'Are you ready to make history?'" Kaufman said, "She had a complete response and is still free of tumor today. She had a little kid at the time. I recently got an email from her—the kid is in college now."

CREDIT: HOWARD KAUFMAN

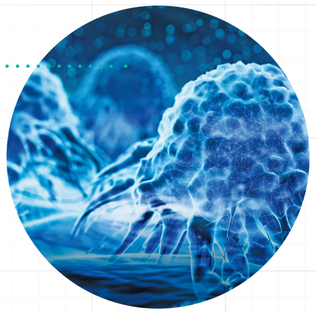
Howard Kaufman led the phase II and III trials for treating melanoma with T-VEC, which became the first FDA-approved oncolytic viral therapy.

2016–PRESENT — Unlocking new avenues

The approval of T-VEC generated excitement in the viral therapy field and led to further exploration of novel therapeutic strategies and combinations. Researchers found that oncolytic viruses have a unique ability to convert cold tumors, which typically evade immune system attacks, into hot tumors that are more susceptible to immunotherapy. Numerous ongoing clinical trials researchers are investigating the efficacy of oncolytic viruses in combination with immunotherapies like immune checkpoint inhibitors, which have shown promising results and improved patient outcomes.

"We're now getting better at designing the viruses upfront for better lytic activity against cancer," Kaufman said. "We're also adding better payloads into the virus." These payloads include a variety of transgenes such as cytokines and immune modulators that enhance the virus's ability to stimulate the immune system. For example, some researchers are incorporating genes encoding interleukin-12, a potent cytokine that boosts the activity of T cells and natural killer cells, while some are arming viruses with the ligand for cluster of differentiation 40, an immune stimulator that enhances B cell activation (15).

Researchers are also exploring more effective delivery methods, such as intravenous administration, for oncolytic viruses. Building on the development of ONYX-015, Kirn has been creating new viral therapies that can safely circulate through the bloodstream to effectively target metastatic and distant tumors. "The next step is to unlock the full potential of oncolytic virus therapy," Kirn said.



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Researchers are exploring better virus designs and more effective delivery methods to target difficult-to-treat cancers such as metastatic tumors.

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