China Approves World’s First Oncolytic Virus Therapy For Cancer Treatment

Oncolytic virus research got a welcome boost last November when Chinese regulators approved the world’s first oncolytic viral therapy for cancer, Shanghai Sunway Biotech’s genetically modified adenovirus H101.

“It’s fantastic for the field,” said John Bell, Ph.D., of the Ottawa Health Research Institute in Canada. “We needed to have something that was a success, and so I think this is a good first start.”

Oncolytic viruses are live viruses that selectively kill cancer cells. Shanghai Sunway Biotech expects to begin marketing H101 in July for treating head and neck cancer. The company is also testing the virus in lung cancer and has bought the rights to Onyx-15, an almost identical virus that Onyx Pharmaceuticals took into phase III trials in 2000 but later dropped after its marketing partner bailed out.

Now the Chinese effort has breathed new life into the Onyx virus. Sunway’s next step, says company president Hu Fang, M.D., is to compare it with H101 in a Chinese trial. The company will then apply to test one of the viruses in Europe and the United States. “The first choice is Onyx-15, but we can’t exclude the H101,” Hu said.

Virus Interruptus

The Chinese resurrection of Onyx-15 gives it a second chance after the aborted U.S. run that began in 1996. That year, Onyx biochemist Frank McCormick, Ph.D.—now the director of the University of California, San Francisco, Comprehensive Cancer Center—had the idea that an adenovirus without its E1B gene, which inactivates the host cell’s p53 gene, would selectively kill cancer cells. That’s because normal cells harboring the modified, defenseless virus would be subject to p53-mediated cell cycle arrest, preventing the virus from replicating. Cancer cells lacking p53 would be unable to halt viral replication and would be lysed, with the multiplied viruses bursting out to infect and destroy the entire tumor.

McCormick’s hypothesis was brilliant, but incorrect. It soon became clear that Onyx-15 was not specific for p53-null cells. But in early human trials, for then-unknown reasons, it still killed tumor cells preferentially and was superior to chemotherapy alone. Sunway’s H101 results, therefore, did not come as a surprise. In its phase III trial, Sunway reported a 79% response rate for H101 plus chemotherapy, compared with 40% for chemotherapy alone. “Those results are very similar to what we would have predicted with our phase III trial,” said David Kirn, M.D., who helped develop Onyx-15 and who now heads Jennerex Biotherapeutics in Mill Valley, Calif.

That trial barely got off the ground before it was suspended in 2000 by Pfizer, which had just acquired Onyx’s development partner, Warner-Lambert. Without funding to complete the trial on its own, Onyx discontinued the program.
Kirn believes that complete phase III results would have led to U.S. Food and Drug Administration approval for Onyx-15. The virus “would have been made obsolete very quickly by much better viruses,” he said, “but … it would have been approved.” Such approval, he added, would have been “huge” for the field. Instead, the field was stigmatized, since many people assumed Onyx-15 didn’t work. “There’s this mistaken impression out there,” said Kirn. “In fact, the phase III was never done.”

**Final Judgment**

Sunway has now indirectly validated the Onyx approach. Hu, a former postdoctoral fellow in the laboratory of Michael Thaler, M.D., at the University of California, San Francisco, was fully aware of Onyx-15 when he formed Sunway Biotech in 1997. The company slightly modified the virus to obtain a patent in China and in 2000 began human testing. The only difference between the Chinese and American viruses is a slightly larger deletion in H101’s E3 gene, which affects immune response.

Part of H101’s success may be due to not treating manageable patient fevers in the phase III trial. After observing a high rate of responses in such patients in a phase II study, Hu reasoned that higher body temperature should aid viral replication and enhance the anticancer immune response. (Recent laboratory studies in the United States back this theory.)

Despite H101’s enhanced response rate over chemotherapy alone, the ultimate test of a drug’s worth is patient survival. Unfortunately, Sunway has not reported survival data because Chinese regulators at that time based their review on objective response rate, not survival. And although the company intends to report survival data, it can follow only a subset of the 140 evaluable patients in the phase III trial, because many of Sunway’s patients live in isolated rural areas and are never seen by their doctors again.

“This is our weakness in this clinical trial,” acknowledged Hu, who added that all current and future trials will have survival endpoints and plans for following up with patients. Approval for either H101 or Onyx-15 in Europe and the United States will depend on improving patient survival. Only then will final judgment be possible for these two adenoviruses.

**A Rebounding Field**

Onyx-15, in retrospect, was not the ideal oncolytic virus. For one thing, the E3 deletion probably hurt Onyx-15’s potency. “In the early days, we were all pretty naïve,” said Kirn. “We thought, ‘Boy, viruses replicate so fast, and they produce tens of thousands of virions per cell [so] you can just shoot an adenovirus in there and infect a few cells and eradicate the whole thing.’”

Onyx scientists chose an E3-deleted adenovirus mutant off the shelf, not realizing their mistake until years later. “It definitely leads to more rapid clearance of the virus,” said Kirn.

Although some companies and labs continue to work with adenovirus, much of the field has switched to other viruses. “Adenovirus, it turns out now in retrospect, had a number of fundamental flaws,” said Kirn. “It spreads very slowly … and the packaging capacity to express other genes is extremely limited.” Also, adenovirus works poorly when given intravenously. Such systemic delivery is the field’s holy grail, since injecting the virus directly into primary tumors—the H101 and Onyx-15 approach—is unlikely to infect and eliminate distant metastases. “The real challenge, in cancer in general, is to get [at] disseminated disease,” said Bell. “That’s where we’re really not being successful.”

Oncolytic viruses have met that challenge in preclinical studies by eliminating metastases in animals. “We just have to move now into humans,” Bell said. He added that he hopes to eventually accomplish this move with vesicular stomatitis virus (VSV), an enveloped RNA virus that is not a human pathogen. Since VSV is sensitive to the innate immune response triggered by interferon, Bell reasoned that tumors, which evolve to become resistant to the interferon response, should be a safe haven for VSV replication, whereas VSV in normal cells would be suppressed. Using VSV mutants unable to shut down the interferon response, Bell showed in 2003 that his viruses could eradicate advanced tumors in xenograft mouse models.

Meanwhile, Jennerex is moving its genetically modified vaccinia viruses into studies in humans. Vaccinia has been used over the last century to inoculate humans against smallpox, and, like VSV, vaccinia is inherently oncolytic, replicates efficiently, and can be delivered intravenously. Jennerex has added a gene coding for granulocyte–macrophage colony-stimulating factor (GM-CSF) to stimulate immune response to the tumor and deleted the gene for thymidine kinase, required for viral replication in normal cells (but not tumors). A phase I study of one such virus at Thomas Jefferson University in Philadelphia found that five of seven patients with metastatic melanoma had an objective response at the injection site, including one complete response. Some noninjected tumors also shrunk. Jennerex is now testing this virus in cancer patients with a variety of tumors. Newer versions with additional tumor-targeting qualities should enter the clinic this year.

**Overcoming Obstacles**

Several other academic groups and small companies have oncolytic viruses in phase I studies or late preclinical development. The main obstacle for all these therapies is the human adaptive immune response, because antibodies invariably mobilize against the oncolytic viruses themselves. Can the viruses kill tumors faster than the body’s immune system kills the viruses? “That’s the big question,” acknowledges Kirn. If the viruses fall short, giving drugs to suppress B cells, or using multiple different oncolytic viruses in succession, are possible solutions.

Safety concerns about virulent strains arising during viral replication in tumors
have not entirely disappeared. Nor has the memory of the massive immune and inflammatory reaction that killed Pennsylvania teenager Jesse Gelsinger in a 1999 gene therapy trial using an adenoviral vector. But recent human oncolytic virus trials have shown consistent safety, with most unable to even reach the maximum tolerated dose. Immune and inflammatory responses, Bell pointed out, are monitored especially closely, with at least one company using small doses of virus to desensitize patients to side effects before administering the therapeutic dose.

With the success in China, the newer viruses will have more chances to prove their worth in the clinic. “The people who’ve stuck with it are now developing things that are going to … have much greater impact than the local administration of an adenovirus,” said Kirn. “It’s an exciting time in the field.”

—Ken Garber

© Oxford University Press 2006. DOI: 10.1093/jnci/djj111