ONCOLOGY

Will a Twist of Viral Fate Lead To a New Cancer Treatment?

When Frank McCormick first started daydreaming about the devious means by which a common respiratory virus co-opts law-abiding cells for its own purposes, he wasn't thinking about cancer. But as he pondered those stratagems, this biochemist from ONYX Pharmaceuticals in Richmond, California, realized that they suggested a way to outsmart the virus and turn its destructive talents to advantage. Now, barely 4 years later, he and his colleagues may be on the way to using a modified version of the pathogen, a member of the adenovirus family, to treat cancer.

On page 373, McCormick and his colleagues at ONYX describe how an adenovirus that has a key gene deleted can no longer reproduce itself in normal cells but does just fine in cancer cells lacking the *p53* tumor suppressor gene. As a result, the virus kills the cancer cells, apparently without harming the normal cells, and it can also inhibit the growth of *p53*-deficient human cancers transplanted into mice. The next step—a clinical trial in human cancer patients—is already under way. And the work has titillated the cancer research community. "What I like is how clever it is," comments Richard Klausner, director of the National Cancer Institute in Bethesda, Maryland. "It's been a long-held fantasy to find an [anti-cancer] virus."

Even more exciting is the fact that the virus targets cells with ineffective *p53*. The loss or inactivation of this gene is thought to contribute to the development of 50% of all human cancers, including such common ones as breast, colon, and lung cancers. As a result, the virus might be widely applicable in cancer therapy, especially because loss of *p53* also helps make cancers resistant to more conventional chemotherapeutic drugs. Still, as Klausner points out, there is no guarantee that the new viral therapy will pan out. "Not every [new cancer treatment] that's clever and targeted [to tumor cells] will wind up being useful," he cautions.

Indeed, it has already taken many years—and a bit of luck—for researchers to recognize that adenovirus might have cancer-fighting potential. The saga started in 1977 when virologists discovered that the *E1B* region of the adenovirus genome is essential for viral reproduction and that it codes for a protein that binds to the p53 protein. The significance of that binding wasn't understood at the time, however, because little was known about p53's function.

Not until the early 1990s did researchers learn that when p53 is present and working correctly, it prevents cells from duplicating either damaged DNA or foreign DNA that might have slipped in, such as that from viruses. It does this by halting cell division until the damaged DNA is repaired, or in some cases, by causing the cells to undergo programmed cell death. To get a cell to replicate the foreign DNA, a virus has to shackle the p53 protein—and molecular biologist Arnie Berk of the University of California, Los Angeles (UCLA), and his colleagues showed that the E1B protein does just that job for adenoviruses, allowing infected cells to divide. Such infections kill the cells, but the immune system limits the damage by clearing the virus from the body.

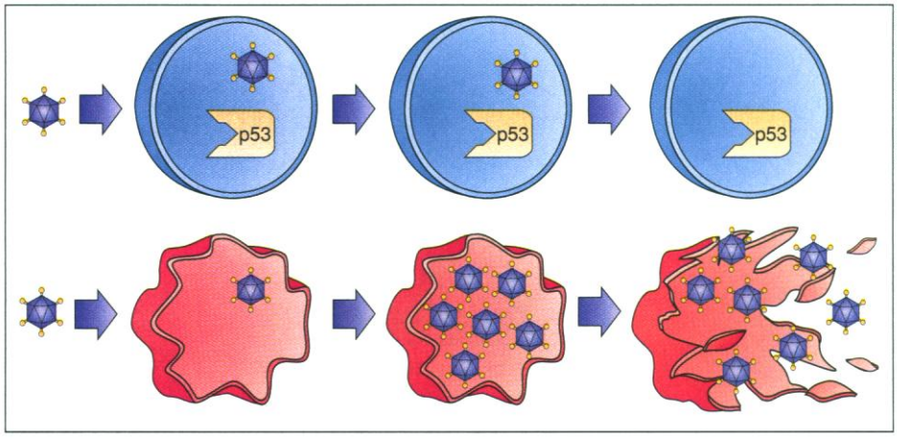
At about the same time, scientists learned that *p53* also has a role in cancer: If a mutation inactivates this gene, cells with damaged DNA can continue to divide and, in doing so, pile up other gene mutations that can lead to cancer. And that's when McCormick began getting interested in adenovirus.

McCormick wondered how the virus would behave in a cell that lacked the known E1B target, p53. "I realized that [the cell] would be a cancer cell," McCormick recalls, and he began to see the potential of using a mutant virus to fight cancer. Because adenoviruses must turn off p53 in order to replicate, he realized, any virus that could not disable p53 would be unable to grow in healthy cells, but it could wreak havoc in cells lacking p53—which is to say, in a wide variety of cancer cells. "If it worked, it would be the ideal cancer therapeutic," he thought.

His group combed the literature for such a mutant, coming up with about a dozen that other researchers had made through genetic engineering and which lacked either E1B or another region needed for viral replication, designated E1A, or both. They tested these and decided on one (designated dl1520) that Berk had produced in 1987. With the help of Berk's colleague Carol Eng, McCormick's team got started in earnest, testing the virus's ability to grow in normal skin cells and in about 20 different kinds of tumor cells lacking p53, including cells from cervical and colon cancers. The findings were encouraging, McCormick says: "In tumor cells it grows very much like the normal virus and has the killing power of the normal virus, but it grows very poorly in normal cells."

Even more promising results came from animal studies. The ONYX team put human tumor cells under the skin of mice that were specially bred to lack an immune system and thus couldn't reject the foreign tissue. Once the cells had produced substantial tumors, the researchers injected the mutant adenovirus directly into the tumors. Three of the five tumors disappeared altogether and didn't reappear during the 3 months the animals were studied, and one other got smaller. Based on this and other work, the ONYX group estimates that if an injection can infect 2% of the tumor's cells with virus, the virus will do the rest, spreading to the rest of the tumor and eventually killing it.

Buoyed by these findings, the ONYX team was able to get approval from the U.S. Food and Drug Administration for a preliminary safety test of the virus in people with head or neck cancers that have not responded to conventional therapies. The trials, which are being conducted by Daniel Von Hoff, an oncologist at the University of Texas Health Science Center in San Antonio, and by Allan Balmain at the University of Glasgow in Scotland, should be finished



ONYX PHARMACEUTICALS

Discriminating virus. Lacking the protein that shuts down p53, the mutant adenovirus can't reproduce in p53-bearing cells *(top)*, but destroys cancer cells lacking p53 *(bottom)*.

sometime in 1997. So far, the virus, which is injected directly into the patients' tumors, appears safe. In Texas, four sets of patients, a total of 12 in all, have received the injections, and no side effects have appeared, even with the higher doses. That's "rare" for new cancer treatments, Von Hoff says. "Usually by now we'd see some fever or chills."

Still, it's too early to tell whether the injections are producing any therapeutic effects. And other researchers point out that the mice the McCormick team used to test the virus's anti-tumor effects may not be a good model of human patients. For one thing, the animals lacked immune systems, and therefore the studies could not address whether the body's immune system will get in the way of any therapeutic effects. Most adults have already been infected by adenoviruses, Klausner points out, and as a result they have immune systems that are primed to destroy the virus, possibly before it has a chance to spread throughout a tumor. Inactivation of the virus by the immune system has hindered efforts to use adenovirus in gene therapy, for example. "That's been a real problem," McCormick admits.

Also, says Berk, "[the virus's] therapeutic value depends on the ability to discriminate between cancer cells and normal cells." Because adenovirus does not infect mouse cells, the mouse studies do not indicate whether the infection will be restricted to the tumor. And there are reasons to suspect that it might not be. Studies conducted 20 years ago with different mutant adenoviruses indicated that sometimes viruses lacking E1B do grow in certain cells containing p53, such as human embryonic kidney cells, so it may be that the cell-killing virus would not restrict itself to cancer cells. Conversely, in other tests, mutants like dl1520 failed to thrive in cervical cancer cells lacking the p53 protein. These somewhat contradictory findings suggest "the story is much more complicated" than the ONYX researchers think, says Berk, and that the virus might not be as effective or as discriminating as they hope.

And even if the virus works, delivering it to a deep or inaccessible tumor, let alone to any distant metastases, could be a challenge. "The real issue is how to get the virus to a particular site," McCormick says. Consequently, for the time being, the viral treatment can be tried only against tumors in the head, neck, brain, ovaries, and cervix, tissues into which virus can be directly injected.

But if the virus really can selectively kill cancer cells, even if only for a few kinds of tumors, "it will be a godsend," says pediatric oncologist Michael Kasten of The Johns Hopkins Hospital in Baltimore. "I can't wait to see how it works in people."

–Elizabeth Pennisi

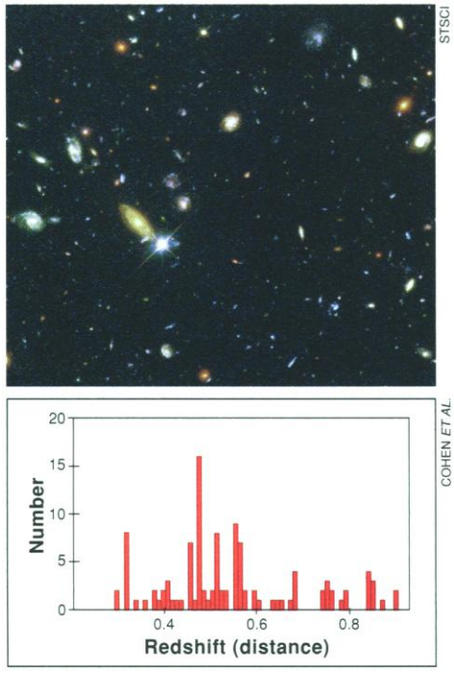
ASTRONOMY

Goodness Gracious, Great Walls Afar

A portrait of the early universe has gained a third dimension and a new element of mystery. Last December, scientists pointed the Hubble Space Telescope at the same spot near the Big Dipper for 10 days straight—an exposure so long that it revealed some of the faintest objects ever seen, many of them early galaxies (*Science*, 26 January, p. 450). But two-dimensional pictures rarely do justice to a landscape. Now California Institute of Technology astrophysicist Judith Cohen and her colleagues have determined distances to some of the galaxies in the image, called the Hubble Deep Field, and found that they aren't evenly distributed in space. Instead, as the observers report in the 1 November *Astrophysical Journal*, the galaxies are grouped in discrete structures—perhaps filaments, sheets, or walls.

Astronomers are used to such giant structures in the nearby universe, but at such great distances—about 6 billion light-years away, when the universe was roughly half its present age—a lumpy universe makes theorists uncomfortable. Their scenarios of how the universe evolved generally imply that large structures could not have formed until more recently. Cohen and her team ran into skepticism this spring when they reported evidence for distant structures in another patch of sky (*Science*, 14 June, p. 1590). But the latest measurement, she says, suggests that the previous observations were not a fluke and "structures at this distance are widespread."

To determine the distances of Deep Field galaxies, Cohen and her colleagues had to gather enough light from each one to make a spectrum and determine the light's redshift—an astronomical measure of distance. Using the powerful 10-meter Keck Telescope in Hawaii, they did so for 140 objects in and around the Deep Field. The group found that the redshifts seemed to cluster in six peaks, with relatively empty stretches between. The authors speculate that their line of sight may have punched through distant walls of galaxies similar to ones observed much closer to our sun.



Wall marks? Clustered redshifts in galaxies seen in the Hubble Deep Field *(top)*.

If the team really has found large-scale structures, says Joseph Silk, an astrophysicist at the University of California, Berkeley, "that would be an interesting constraint" on cosmological theories—especially if the structures are walls, which are more highly organized than clusters or strings. Many current theories assume that matter in the universe is dense enough for structures like the ones seen today to coalesce in short order, implying that structure formation somehow got delayed until recently. If the process started earlier, it must have proceeded more slowly, explains Ray Carlberg, an astrophysicist at the University of Toronto, implying that the universe is less dense than is widely assumed.

But not everyone is convinced that Cohen is really seeing early walls. Carlberg says it's too soon to say exactly what the clustered redshifts represent, because the scientists' data stab through a limited patch of sky. (It would take nearly 250 such patches to cover the full moon.) Such surveys are like "skewers through the universe," adds David Koo, an astrophysicist at the University of California, Santa Cruz, and it's not easy to extrapolate a large-scale structure from one stab. "It's difficult to tell whether they've hit a meatball-like cluster or a sheetlike wall," he says. The authors acknowledge such limitations, and they are surveying adjacent patches to see if the putative walls continue across the sky.

Even if these stabs are not conclusive, astronomers agree that the wider picture should be visible soon. Several other projects are under way at Keck, including an ambitious effort called the Deep Extragalactic Evolutionary Probe, which will use a yet-to-be-built spectrograph to map the redshifts of thousands of galaxies at about the same distances as the ones Cohen observed. Carlberg predicts success. "They have the Keck, and that's the biggest hammer around," he says. "They are going to clobber this problem."

–Gretchen Vogel