

ments in which McKeon and Caput deleted the *p73* gene in mice suggest another possibility: It may be “developmentally important,” he says, especially in the brain and immune system, although how remains to be clarified.

If *p73* is a tumor suppressor, it may behave somewhat differently than *p53* and other previously discovered tumor suppressors. Classic tumor-suppressor genes require two “hits” to be inactivated—a partial or complete deletion of one of the two gene copies, for example, and another, lesser change that cripples the second copy. But Caput, McKeon, and their colleagues have evidence that one *p73* copy is already inactive in normal cells—the apparent result of a mysterious process called imprinting. Its precise function isn’t known, but during embryonic development, imprinting alters certain genes so that the copy inherited either from the mother or the father is specifically shut down.

If one *p73* copy has been silenced by im-

printing, then only one hit—loss of the active copy—might be all that it takes to tip a cell into the uncontrolled growth of cancer. Says Kaelin, “*p73* may be the first example of a new paradigm for how tumor-suppressor genes are involved in cancer.”

Indeed, molecular biologist Rogier Versteeg of the Academic Medical Center in Amsterdam, the Netherlands, has evidence that an imprinted gene may be involved in neuroblastoma development. He has identified two sites of chromosome damage that contribute to neuroblastoma by knocking out as-yet-undiscovered tumor-suppressor genes. Both lie in the same region of chromosome 1 where *p73* is located, and one illustrates “a strong bias” toward loss from the maternal copy of the chromosome in the cancer cells. This bias implies that this specific copy is the active one and must be lost to cause the cancer.

Other work from the Caput-McKeon team suggests that this mystery tumor-suppressor gene may be *p73*. When they looked for the

gene in neuroblastoma cell lines, they found that one *p73* copy had been lost. And while they couldn’t uncover any mutations in the remaining copy, most of the cell lines made no detectable *p73* protein, implying that the second copy had been silenced by imprinting.

In spite of the differences in the roles of *p53* and its new cousin, both in normal cells and in cancer, the family resemblances may be strong enough for them to substitute for each other. If so, says MIT’s Jacks, cancer might be treated by finding a way to switch on *p73* in tumor cells that have lost *p53*. “Even if *p73* is not normally involved in tumor suppression, maybe it could be recruited,” says Jacks. Now McKeon and Caput are searching for further family members. But the discovery of *p73* is already certain to captivate their peers.

—Steven Dickman

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## AIDS RESEARCH

# HIV Gets a Taste of Its Own Medicine

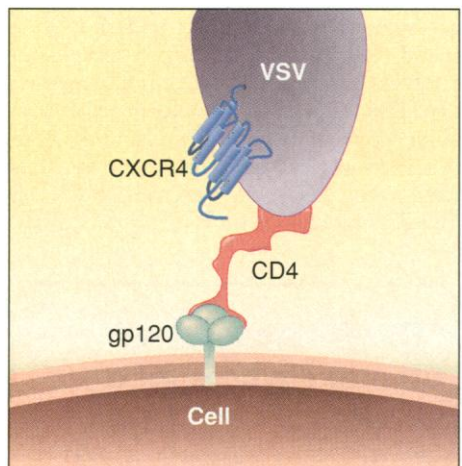
In an attempt to fight fire with fire, researchers have engineered a virus that usually infects cattle to attack the AIDS virus in humans. The innovative approach has so far shown promise only in test-tube experiments, but it is attracting widespread attention among AIDS researchers. “It’s really on the verge of a breakthrough,” says Nava Sarver, who oversees development of novel AIDS treatments at the National Institute of Allergy and Infectious Diseases (NIAID).

Yale University virologist John Rose and co-workers describe in the 5 September issue of *Cell* how they have constructed a potential HIV treatment by modifying vesicular stomatitis virus (VSV), which farmers detest because it causes a mouth infection in cattle that prevents them from eating. As the Yale researchers’ experiments show, their newfangled VSV selectively targets and destroys HIV-infected human cells. “It’s a pretty interesting way of harnessing a virus for peaceful purposes,” says the University of Pennsylvania’s Robert Doms. “It’s a very clever approach.”

The work builds on recent discoveries made by Doms and others about a two-part handshake between HIV and the cells it infects. After HIV binds to the CD4 receptor on a white blood cell, it also must link to another molecule found on the cell’s surface, known as a chemokine receptor. Once these handshakes are complete, HIV gains entry, and shortly thereafter, new virus proteins make their way to the cell’s outer coating, where they stick out like a flag of victory.

Rose and colleagues reasoned that if VSV

could be induced to express these receptors on its surface, they would bind to the HIV proteins displayed on infected cells, turning VSV into a kind of guided missile. To test this idea, the researchers stitched into VSV the genes that code for CD4 and one of HIV’s favored chemokine receptors, CXCR4, and added their engineered VSV to a culture



**Trojan horse.** CD4 and CXCR4 receptors expressed by genetically engineered VSV bind to HIV’s gp120 protein on surface of infected cell.

containing HIV-infected cells. The virus did, indeed, target just the infected cells, killing them rapidly. “VSV is so fast,” says Rose—much faster than HIV, he notes.

A potential downside to this approach is that the modified VSV might kill cells that aren’t infected by HIV. Rose believes that won’t happen because he has stripped VSV

of its own surface protein, which is what allows it to infect a broad range of cells. “Without its normal coat, it can’t infect anything,” says Rose. But only animal tests will provide evidence of that, cautions NIAID director Anthony Fauci.

Although Fauci has high praise for the concept’s ingenuity, he is concerned that it might take an impractically high dose of the modified VSV to make a real dent in a person’s HIV levels. Another worry, says monkey researcher Ronald Desrosiers of the New England Regional Primate Research Center in Southborough, Massachusetts, is that the body will quickly develop an immune response against VSV, limiting its ability to attack HIV.

Still, Sarver, Fauci, and others are anxious for Rose and colleagues to put their viral guided missile to more stringent test-tube and animal tests. Desrosiers already has begun working with Rose to test the concept in monkeys that have been infected with SIV, HIV’s simian cousin. Desrosiers expects to have results in the next few months. Even if they are positive, however, human trials will require the approval of the Food and Drug Administration, which has shown great caution in the past about putting potentially therapeutic viruses into people.

Rose’s strategy is not limited to attacking HIV. NIAID’s Sarver suggests that if researchers can swap different receptors into this “guttled” VSV, the precisely targeted viruses could be used in everything from vaccines to gene therapies to cancer treatments. “We’re not there yet,” says Sarver, “but the potential applications are enormous.”

—Jon Cohen