Researchers knock down gene to stop HIV in its tracks

Last month, San Francisco officials granted a city proclamation to Gero Hütter for his 2007 discovery that a bone marrow transplant could, it seems, cure a person of HIV. The German hematologist's findings raised hopes for a new therapeutic treatment, but the shortage of tissue-matched donors has prompted some researchers to apply the lessons learned to new techniques.

The HIV-resistant bone marrow donor in Hütter's study carried a rare mutation in the gene encoding C-C chemokine receptor type 5, or CCR5, a surface protein essential for helping HIV attach and infect healthy cells (*N. Engl. J. Med.* **360**, 692–698, 2009). The absence of this molecular portal makes infection nearly impossible. However, individuals with the CCR5 mutation are rare, and their bone marrow is not always a good match for all recipients. To emulate the protection of this mutation, several research teams are devising ways to downregulate the expression of CCR5 so that HIV does not recognize and invade sensitive cells in susceptible individuals.

One line of attack involves RNA interference. Last month, for example, Irvin Chen and his colleagues at the University of California–Los Angeles School of Medicine reported that short hairpin RNA could successfully knock down CCR5 expression in human induced pluripotent stem cells (*Hum. Gene Ther.* doi:10.1089/hum.2010.050, 2010). Chen, backed by a $20 million grant from the California Institute for Regenerative Medicine (CIRM), has now partnered with the Tuscon, Arizona–based biotech startup Calimmune to develop therapies based on the approach.

Another strategy takes advantage of a newly developed technology based on zinc finger nucleases. With this approach, pioneered by Sangamo Biosciences of Richmond, California, engineered enzymes make precise cuts in the genome to disrupt gene function. In 2008, Carl June's team at the University of Pennsylvania in Philadelphia used zinc finger nucleases to disrupt CCR5 expression in human T cells, which they injected into HIV-infected mice. The gene therapy lowered viral loads and increased T cell counts in the mice (*Nat. Biotech.* **26**, 808–816, 2008).

Sangamo, in collaboration with June, has since started extracting mature T cells from HIV-positive individuals, knocking down expression of the *CCR5* gene with zinc fingers, and then re-infusing the cells back into the blood. Preliminary results from their first patient indicate that the modified cells are tolerated and persist at stable levels.

Mighty marrow

The T cell approach, however, offers only a treatment—not a cure. So other researchers are focusing instead on altering bone marrow stem cells to provide an everlasting resistance to HIV. Last year, CIRM funded a team led by John Zaia at the City of Hope in Duarte, California, in collaboration with Sangamo, to start pursuing preclinical research applying the same gene therapy tactic in bone marrow.

Jerome Zack of the University of California-Los Angeles AIDS Institute notes that bone marrow stem cell therapy has the advantage of potentially lasting a lifetime, unlike gene therapy aimed at T cells, which must be repeated over and over again after the mature immune cells die out. What's more, says Zack, who is not involved in these studies, bone marrow transplants should help achieve higher cell counts.

"We do not lack ways to attack HIV," says David Strayer, a virologist at Thomas Jefferson University in Philadelphia. "We lack ways to deliver genes adequately."

A potential obstacle to CCR5-based gene therapy is that the protein is not the only receptor recognized by the virus—some viral strains bind the CXCR4 chemokine receptor instead. So June and his colleagues are also developing zinc finger nucleases that target CXCR4. However, some scientists have increased concerns about this approach's safety, because the receptor may have an important role in healthy cells to attract white blood cells to sites of inflammation or injury. "The problem is that [CXCR4] may be more important to the cell for its normal functions than CCR5," says Ramesh Akkina, who studies HIV gene therapy at Colorado State University in Fort Collins. What's more, even strains that normally rely on CCR5 can evolve to use CXCR4 instead.

Instead of focusing solely on these receptors, Zaia also recently completed a phase 1 trial of an HIV gene therapy technique involving three genes—two that interfere with viral replication and one that blocks CCR5. Reporting last month, Zaia's team showed that patients with AIDS-related lymphoma expressed the modified genes in their blood and showed no signs of short-term toxicity (*Sci. Trans. Med.* **2**, 36ra43).

Gene therapy against HIV "is now within the realm of feasibility," says Zaia. "Now we can design larger studies and figure out ways to improve it."

Janelle Weaver, San Francisco

Canadian beacon

Each year, around a million Americans purchase cheap medicines from online Canadian pharmacies to help make ends meet. According to the Canadian International Pharmacy Association (CIPA), which surveyed its 14 member pharmacies for the 15 best sellers to US consumers in 2009, most people who turn to Internet drugstores north of the border are buying everyday prescriptions to treat common chronic conditions, such as heart disease, diabetes and arthritis.

"This is the mainstay of our business," says Tim Smith, CIPA's general manager. "The bulk of our patients are people who are living on fixed income; they're concerned about the high cost of drugs, and they have concerns about their ongoing medical conditions."

Here, in no particular order, are the top selling drugs: