

## How HIV Thwarts a Natural Human Defense

by Kristen Kresge

Scientists now know that human cells have a way to defeat HIV. Following a landmark paper from Michael Malim's laboratory published in *Nature* in 2002, virologists began feverishly studying a protein that protects human cells from HIV infection. The anti-HIV protein is now known as APOBEC3G, found largely in human immune cells — the primary target of HIV infection.

After a virus enters a healthy cell, it co-opts the cell's machinery to produce infectious copies of itself. For years, researchers have known that an HIV protein called Vif — for virion infectivity factor — was essential for the virus to thrive. Now it appears that Vif overcomes the cell's protective APOBEC3G protein. Scientists are seeking to understand the critical interaction between the two, and this discovery may open up new possibilities for HIV treatment.

"When this gene was identified, everybody jumped into the fray," said Ann Sheehy, the post-doctoral fellow in Malim's lab who is credited for the critical work that led to the gene's discovery. Her efforts culminated in *Nature's* editors approaching her to publish her findings. "It's the post-doc everyone dreams about," she added. "When *Nature* asks you to publish, you're ready."

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Drug resistance was a hot topic at the 11th Retrovirus Conference. Find out what ways HIV doctors recommend to avoid the resistance quandary.

## A Gene in a Haystack

Sheehy joined Malim's lab to answer a question that had stymied scientists for 10 years: why some cells required Vif for infection, while others did not. These cells could all become infected with garden variety HIV, but when infected with a modified form of HIV that lacked Vif, some resisted infection. The answer could lie in the genes, but the trick was to narrow the search. Sheehy painstakingly compared two sets of closely related cells that differed by 200 genes, a small number to cellular biologists. Sheehy managed to narrow the candidates to just 10. Still, it took three years to isolate the gene that stopped HIV infection in one group of cells. Identifying this gene was a pivotal discovery.

Once the gene was revealed, researchers quickly identified its corresponding protein, APOBEC3G. Although APOBEC3G's precise function is unclear, the protein appears to protect cells from viruses by radi-



Ann Sheehy is a Senior Research Associate in the Department of Infectious Diseases at King's College London.

cally altering their genome. The alterations are so lethal that the virus no longer functions. For some reason, Vif was preventing APOBEC3G from doing its job.

Sheehy set out to explain why. Through a series of experiments, she found

that Vif bound to APOBEC3G and escorted it to the cell's recycling bin, known as the proteasome. Her next task was to clearly explain this process. Before she could, Xiao-Fang Yu at Johns Hopkins published an elegant series of experiments in *Science* identifying a third critical component: a "giant protein complex," dubbed Cullin 5, that was tagging APOBEC3G for destruction (see figure on next page). Other groups are currently confirming his work. Yu's lab has identified several parts of this structure, all of which represent new targets for drug development.

## Several Targets

To disrupt the interaction between Vif and APOBEC3G, a drug could interfere at three points: binding to Vif, to APOBEC3G, or to any protein on the Cullin 5 complex. And researchers have different opinions about which avenue will lead to a useful drug.

Dana Gabuzda and her colleagues at the Dana-Farber Cancer Institute in Boston are searching for a Vif inhibitor. Even before APOBEC3G's discovery, Gabuzda began screening drugs to find those with a high affinity to Vif. This early work (funded by the American Foundation for AIDS Research) led to an NIH grant to sift through large libraries of molecules that could stop Vif from binding to APOBEC3G. Finding a drug that prevents this protein-protein interaction is of "highest priority" for Gabuzda and the NIH.

Gabuzda is screening 123 promising compounds provided by the National Cancer Institute. These agents inhibit HIV, but how they do so is unclear. By summer, she expects to have a large-scale assay available to quickly analyze more than 100,000 com-

pounds. If a molecule successfully blocks the Vif-APOBEC3G interaction, pinpointing precisely where the drug acts would then require more experiments. "Finding a drug that targets Vif would be ideal because then there would be less concern about side effects in the host," said Gabuzda.

But others contend that a drug directed against Vif will pressure HIV to form resistance, a problem with the current classes of antiretroviral drugs. "If you target viral proteins, they can come up with many ways to become resistant," according to Roger Pomerantz at Thomas Jefferson University.

For this reason, Nathaniel Landau of the Salk Institute favors a drug to protect APOBEC3G. In a paper recently published in the *Proceedings of the National Academy of Sciences*, Landau's group asserts that the amino acid numbered 128 in APOBEC3G could be a site of direct contact with Vif. "If you have a drug that works against APOBEC3G, it has to block Vif but still allow APOBEC3G to have activity. You don't want to entirely block the antiviral activity of APOBEC3G," said Landau, who sees potential for a small molecule that binds at amino acid 128.

Bryan Cullen's group at Duke University conducted similar experiments, but reached a different conclusion. Cullen agrees that amino acid 128 plays a role in the interaction, but not directly in binding to Vif. He postulates that a change there interferes with forming a larger complex. He bases this suggestion on previous studies by Michael Neuberger that reported that a larger site on APOBEC3G is necessary for binding — not including amino acid 128. The results from Cullen's work will also appear in the *Proceedings of the National Academy of Sciences*.

Understanding the binding site, while crucial for drug development, has already begun to inform work on the elusive animal model for HIV. Researchers have also found that the amino acid positioned at 128 differs in other animals, so Vif cannot bind to their APOBEC3G proteins. This partly explains why mice or monkeys cannot be infected with HIV, a major obstacle to HIV research. Conversely, it also explains why the Vif protein in the monkey version of HIV (known as SIV) is inactive in humans. "This may help to make a better mouse and monkey model by helping us to design viruses that will replicate in these other species," said Landau.

APOBEC3G may also lend insight to researchers who study long-term nonprogressors — HIV-infected people who do not progress to AIDS. Landau's group will analyze the APOBEC3G of cells isolated from these individuals. The structure or expression of their

protein may contribute to their ability to stall disease. Information gleaned from this population may further inform drug development.

Developing a drug to interact with APOBEC3G requires a novel approach, and even Landau acknowledges its complications. “You have to be careful when you’re talking about targeting cellular proteins,” he said. “Those proteins all have important functions that you don’t want to completely block. It may be toxic and could actually kill the cell.”

A different strategy involves increasing, or over-expressing, APOBEC3G protein in immune cells by chemically activating the gene that makes it. HIV yields enough Vif to overcome APOBEC3G, but if you swamp the system with APOBEC3G, the virus could not keep up, according to Landau. Unfortunately, high levels could also be toxic to the cell. “We don’t really know what APOBEC3G does,” said Pomerantz. “Over-expressing it could have some effects on the human genome. It may be something you don’t want to muck with.”

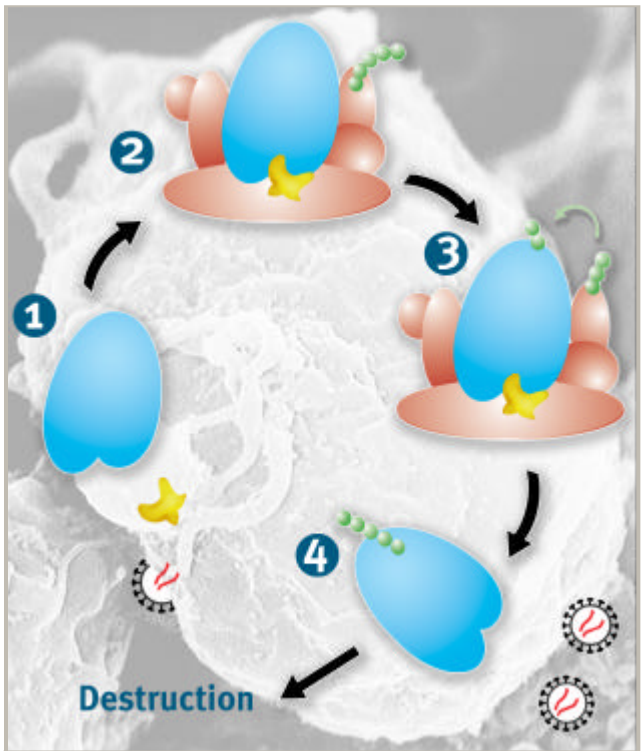
Meanwhile, Sheehy is focusing on the proteins of the Cullin 5 complex. She will begin to look at how these proteins function to determine which of them, when blocked, are least toxic to the cell. Her efforts could lead to the design of drugs that target different parts of the complex and stop it from destroying APOBEC3G. “If you can interfere [with] or perturb any part of the complex, you might be able to prevent the degradation of APOBEC3G,” according to Sheehy.

## Hitting the Bull’s-Eye

Regardless of their approach, scientists all agree that finding a safe, effective drug is a significant challenge — and several years away from human testing. Gabuzda’s lab is currently the only one that is screening compounds, although other groups are preparing to evaluate potential drugs.

The search for an inhibitor guarantees that this field will become more competitive. All groups involved can vouch for the urgency of their work and the rush to publish. Even Sheehy is considering new research areas. With only 18 months of funding remaining from the Royal Society, she won’t miss the competition. “I think I want to do something different after this,” she said.

Soon some of this competition could shift to industry. Pomerantz predicts that drugs that interact at specific sites — referred to as rational drug design — will materialize only when pharmaceutical companies become involved. “Academics design concepts, drug



## APOBEC3G, interrupted

Scientists are starting to understand that cells harbor a defense against HIV — and how the elusive HIV protein Vif defeats it. Vif appears to interfere with a protein that defends the cell from viruses. Here is a model of how Vif counteracts the protein, called APOBEC3G, inside an HIV-infected T-cell.


- 1) Upon infection, APOBEC3G (blue) prepares to disable HIV by making lethal mistakes in its genetic material.
- 2) Instead, Vif (yellow) links APOBEC3G with a protein complex, dubbed Cullin 5 (red).
- 3) The protein complex tags APOBEC3G with small proteins, called ubiquitins, shown here as green beads.
- 4) The ubiquitin “label” prematurely directs APOBEC3G to the cellular trash heap, where it is destroyed. This leaves HIV free to spread.

Understanding the precise interaction of Vif, APOBEC3G, and the Cullin 5 complex will spawn drug development.

companies make drugs,” he said. “They’re the best people to design inhibitors. Merck wouldn’t put money into this until it’s ready for prime time. They’re more interested now.” Both Pomerantz and Sheehy have been approached for access to their patents, though neither would disclose company names.

But industry joining academia in the search does not guarantee immediate success. The struggle to find a drug that targets HIV’s integrase enzyme provides a sobering example. “We’ve known about integrase forever and there are drugs that can inhibit it in the laboratory. But we’ve been trying to get an integrase inhibitor into humans for 20 years,” said Pomerantz.

Yet Vif represents a new frontier in treatments for HIV/AIDS, and with it comes great excitement. An inhibitor would be a welcome addition to the current combination of drug classes. “I have no doubt that this will mean something important for drug development. The question is whether it will take one year or five years until we find something that works,” said Gabuzda.



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## CCR5: A Genetic Mistake Makes Good

by Gunjan Sinha

Around 1,000 years ago, a Northern European man (or woman) was born with a slightly different spelling in his DNA that may have given him a fantastic edge. The misspelling occurred in a gene called CCR5, and it rendered the gene obsolete. Scientists speculate that mutation of this gene helped the person, perhaps protecting him from black plague or another infectious disease common in his day. This person passed the mutated gene to his children, who passed it to their children, and so on, a biological accident that is still making history.

Normally CCR5 acts as a receptor, transmitting messages to the cell’s interior. It also serves as a secondary receptor for HIV to enter cells. HIV infects cells by first attaching to a protein on the cell surface called CD4. It then attaches to a second “coreceptor,” CCR5 (or CXCR4, depending on the virus’s preference, or *tropism*). People born with two defective CCR5 receptor genes live healthy, normal lives — and are highly resistant to HIV that uses the CCR5 receptor, the most common form of the virus. These discoveries in 1996 led scientists down a “remarkably quick” path to developing an entirely new class of drugs to treat HIV, says John Moore of Weill Medical College at Cornell University.

Unlike most antiretrovirals, which act on the virus once inside the cell, CCR5 inhibitors block entry into the cell. They stop HIV even earlier than T-20 (Fuzeon), which permits HIV attachment to both CD4 and CCR5, but subsequently interferes with virus-cell fusion.

Already, three drugs in clinical trials are showing promising results, and more are in development. Although physicians can only speculate about the coming class’s popularity, the need for new drugs has never been more urgent. “About 10% of all new infections today are caused by HIV strains that have some degree of resistance to existing drugs,” says Robert Doms, chair of the Department of Microbiology at the University of Pennsylvania and a pioneer in CCR5 research.

### Nature’s Proof of Principle

In 1996, several different groups discovered the CCR5 receptor simultaneously: researchers at the Aaron Diamond AIDS Research Center (John Moore and Richard Koup), New York University (Dan Littman with Nathaniel Landau at Aaron Diamond), the

National Institutes of Health (Ed Berger), and Harvard University (Joseph Sodroski).

But Ed Berger, then at the National Institutes of Health, “really deserves primary credit for opening up the coreceptor field,” according to Moore. Berger showed that some HIV isolates used the CXCR4 receptor to enter cells, but many more isolates did not. Robert Gallo’s lab provided another clue: that small proteins called chemokines bound to receptors and blocked infections, “basically making it a no-brainer that there was a counterpart receptor,” Moore adds.

Not all of the scientists were studying the complexities of HIV. Some, like Marc Parmentier at Université Libre in Brussels, were more interested in chemokine receptors. In 1996, Parmentier published the first paper describing CCR5.

He had no idea that it might play a role in HIV infection until he got a call from Doms. After seeing the paper, Doms called Parmentier and asked him to collaborate. They tried to infect cells with CCR5 receptors with HIV — and did. “It was the most exciting time of my career,” Doms recalls.

Shortly after the CCR5 discovery, three separate groups analyzed the genes of individuals who, despite repeated exposure, did not become HIV infected. They all came to the same conclusion: HIV resistance related to the kind of CCR5 genes a person carried. People with two mutated CCR5 genes (homozygotes) were extremely resistant. People with one normal gene and one mutated gene (heterozygotes) could get HIV, but the disease progressed more slowly. Moreover, having two mutated genes did not impair a person’s health, suggesting that compounds could interfere with CCR5’s function but cause few side effects. These findings gave drug research a boost. “The fact that people had CCR5 deletions and were still healthy was like nature giving you proof of principle. It suggested that you could

inhibit the receptor safely,” says Robert Consalvo, director of external communications at Schering-Plough Research Institute.

## The Quest for a Pill

As soon as scientists identified the receptor, several pharmaceutical companies launched their search for compounds to block CCR5. Although seven years may seem a long time to find and test such compounds, “the research has actually moved very quickly compared to other research programs,” says Consalvo, which typically takes “ten years or more.”

Schering-Plough has taken two compounds through early clinical trials, SCH-C and SCH-D, although the D compound appears more potent. The company released data on SCH-D at the 11th Conference on Retroviruses and Opportunistic Infections showing that a 10-mg dose taken orally twice a day for 14 days reduced viral loads by an average of 10 fold. (SCH-C required at least 50 mg to slash viral loads to similar levels.) “Its greater potency means [SCH-D] will probably be a once-a-day administration, which is obviously better for compliance,” says Mark Laughlin, Schering’s director of early clinical research and experimental medicine.

People in this trial also showed a strong dose response; taking more of the drug meant suppressing more virus. At 50 mg twice a day, patients saw an average 60-fold drop in their viral load. Schering also reported no significant drug-related side effects: both placebo and drug recipients had similar complaints of headaches, dizziness, and other mild symptoms. “The biggest plus is that we did not see any QTc effects,” says Laughlin, referring to a type of heart arrhythmia that occurred with SCH-C. Schering expects to move only SCH-D into phase II testing later this year.

Pfizer plans to begin phase II studies of its entry inhibitor, UK-427,857, very soon. Results from the company’s phase I trial were similar to Schering’s. In 10 patients who had never taken HIV medication, between 20 mg and 100 mg of Pfizer’s compound taken orally twice a day reduced viral loads by 10 to 100 fold over 10 days, rendering HIV almost undetectable in some cases. Side effects from the drug and placebo were also indistinguishable, says Steven Felstead, research and development team leader for Pfizer in the United Kingdom.

While these results are early, many consider them extremely encouraging. “What I’ve seen of the clinical data suggest that both Schering D and Pfizer’s compound are potent, powerful, and promising

“The fact that people had CCR5 deletions and were still healthy was like nature giving you proof of principle. It suggested that you could inhibit the receptor safely.”

— Robert Consalvo

# Pulling Back the Reins on Drug Resistance

by Elizabeth Paukstis

This year's 11th Conference on Retroviruses and Opportunistic Infections brought a myriad of posters and presentations on drug resistance — what causes it, how long it lasts, and what might work against it. Few would dispute that resistance to antiretrovirals is one of the primary dilemmas confronting HIV-positive people and their providers today.

"It's one of the major issues in the clinic," said Michael Kozal of Yale University School of Medicine. "We're facing it every day, seeing patients with drug-resistant virus and being challenged with how best to treat them."

Kozal presented a late-breaking paper (abstract 35LB) concerning high-risk sexual behavior by a small group of people with drug-resistant virus. He and his colleagues postulated that the practice of frequent, unprotected sex has substantially contributed to the rise in new, resistant infections. His take-home message was clear: condoms, condoms, condoms. And no needle sharing.

Indeed, Kozal emphasized that HIV doctors need to work harder to underscore these messages. "We're seeing the patients who are transmitting the drug-resistant virus in the clinic. There are oppor-

tunities to intervene there: to push for safe-sex behavior and to discourage sharing needles," said Kozal.

Douglas Richman of the University of California, San Diego agreed that safe sex was crucial to dodging drug-resistant infection. "The way to avoid acquiring drug-resistant virus is practicing safe sex," Richman concluded.

Clinicians also offered evidence that once resistant mutations arise, they can persist for years, compromising the effectiveness of treatment regimens. "Resistance doesn't go away," commented Sarah Palmer of the HIV Drug Resistance Program in Frederick, Maryland. "It persists. I've heard people use the term 'transient resistance.' There is no such thing."

Palmer presented data on the endurance of NNRTI-resistant strains of the virus (abstract 37). Using a more sensitive method than a standard genotype test, she and her associates found that mutations resistant to efavirenz (Sustiva) could last up to five years. This study emphasized an important point about resistance in the clinic: that critical mutations persist beneath the radar of available technology, and may be present but undetectable.

inhibitors," comments Moore. (Moore receives research funding from both companies, but no consulting fees.)

## Pressure to Use CXCR4?

Whether these compounds will drive the virus to use the CXCR4 coreceptor concerns these drug makers, because CXCR4-tropic HIV is more pathogenic. Some people who have mutated CCR5 genes do become infected with HIV, almost always with a strain that uses CXCR4. Also, as people progress to AIDS, about half contain some virus that has switched to the CXCR4 receptor. "In over 95% of people infected, the virus first uses CCR5," explains Doms. "Over time, the virus mutates so it can use CXCR4, which is present on many more of your T-cells." After the mutation, a person's health tends to plummet.

Moore has examined receptor switching extensively in cells in culture and found that, while the

virus evolves to tolerate CCR5 inhibitors, "receptor switching doesn't happen." In his studies, the virus gained mutations that enabled it to bypass the inhibitors while still using the CCR5 receptor. "They still use CCR5, but the resistance to any particular class of inhibitor is likely to depend on the nature of the inhibitor binding sites on CCR5, not receptor switching," he says. Although Moore acknowledges receptor switching might occur in vivo, both Pfizer and Schering have early evidence suggesting that their compounds will not pressure the virus to use CXCR4. In its clinical study, Schering enrolled one patient who, researchers later discovered, had dual-tropic virus, a strain that uses either CCR5 or CXCR4 to enter cells. At the end of the 10-day drug regimen, his total viral load still dropped by fivefold. Further analysis showed that the drug had selectively suppressed the CCR5-dependent virus.

Pfizer also inadvertently enrolled someone with dual-tropic virus into its trial. "The patient wasn't

“We typically use standard genotyping to detect resistance, and this is a crude tool,” Palmer explained. “Thirty percent of the virus could be resistant, but the test could miss that. So you may think your patient is susceptible to a drug, but they may not be.”

Once resistance has arrived, “patients have fewer choices,” Kozal stressed. “And they don’t respond as well to therapy.”

Despite the bad news about resistance, clinicians pointed out two bright spots. There are ways to avoid getting infected with drug-resistant HIV; and for those already infected, there are ways to avoid developing drug-resistant HIV.

As John Mellors from the University of Pittsburgh put it, “We have to be careful about what drugs we mix together.” For people already infected, eluding resistance means designing the most potent antiretroviral therapy. A handful of presentations highlighted the failure of certain regimens both to control the virus and to prevent the development of resistance.

Two presentations concentrated on regimens that contain only three nucleosides. Joseph Jemsek of the Jemsek Clinic in Huntersville, North Carolina presented data from a study involving the use of didanosine (Videx), lamivudine (Epivir), and tenofovir (Viread; abstract 51). And Roland Landman of the Hôpital Bichat Claude Bernard in

Paris described a trial that tested abacavir (Ziagen), lamivudine, and tenofovir (abstract 52). Both studies enrolled patients with fairly high viral loads (a median of about 80,000 copies/mL in each trial) and reported high rates of virologic failure. Dangerous resistance mutations — M184I/V and K65R — had also developed in many patients in both trials.

These results led to the consensus that triple nucleoside regimens consistently yield disappointing results, at least in patients with high viral loads. And they underline the importance of a sound treatment regimen. “The way to avoid acquiring drug resistance is to use the best regimen possible, and to adhere to it,” Richman remarked.

Palmer emphasized that this was true especially in regard to a person’s first regimen. “The patient’s first regimen should be the most optimal,” said Palmer. “If it fails, they’re in trouble.”

In addition, Palmer advised patients to obtain a genotype test before they start therapy. Despite this method’s flaws, it allows doctors to ascertain any drugs an individual is resistant to, and then build the regimen accordingly.

While the notion of drug resistance is daunting, clinicians and patients have some means for warding it off. As Kozal asserted, “I think [drug resistance] is here to stay. But hopefully, we can keep it at bay.”

responding to the drug,” recalls Felstead. “We went back to the original samples and found that, at baseline, he had some clones [HIV strains] that were CCR5 dependent, some that were CXCR4 dependent, and some that used both.” But unlike Schering’s patient, this volunteer’s viral load did not decline. Although the drug did suppress CCR5-dependent virus, CXCR4-dependent HIV had multiplied to fill the gap. “In the absence of competition, CXCR4[-dependent virus] appeared to increase,” Felstead adds. He conjectures that the different outcomes may have depended on how efficiently the CXCR4-dependent viruses replicated; Pfizer’s patient may have had a hardier CXCR4-dependent virus than Schering’s.

“The encouraging thing about both of those observations,” says Laughlin, “is that after stopping treatment, both patients went right back to baseline viral levels. We had been very worried that things would get out of control [with their CXCR4-dependent virus].” In order to fully grasp this issue,

researchers will have to study more people for longer periods.

## Still More to Come

The latest company to develop a CCR5 inhibitor is GlaxoSmithKline, which licensed its compound from Ono Pharmaceuticals of Japan. In a preliminary study to test its compound’s safety in healthy, uninfected volunteers, the company found that people could safely take doses ranging from 50 mg once a day to 800 mg twice a day. They saw no serious side effects or arrhythmia. “It looks like a great compound,” comments Laughlin, who has seen the data. “One thing that interests me is this persistence of antiviral effects after you stop the drug.” Glaxo reported that the inhibitor bound to the CCR5 receptors after 24 hours. “The residual antiviral effects mean that you can reduce the frequency of dosing,” he adds. The company will soon launch a study to test its compound’s antiviral potency in 140 HIV-infected volun-



teers, says Stephen LaFon, HIV project leader at Glaxo.

Other smaller companies are studying inhibitors too, but all are in earlier stages. Most are designing small molecules based on 3-D images of the CCR5 receptor, then screening huge libraries for compounds that fit the receptor snugly enough to block HIV from attaching. One company that is taking a different approach is Progenics Pharmaceuticals, based in Tarrytown, New York. The firm is studying monoclonal antibodies, proteins manufactured from human or animal cells and too big to package into pills.

Monoclonal antibodies carry several advantages, says Paul Maddon, Progenics's CEO and founder. "You can get a much longer half-life and exquisite specificity." The benefit of a longer half-life outweighs the fact that the drug would have to be taken by injection, according to Maddon. The specificity of the antibody also prevents HIV from binding, but does not stop the receptor's normal function, whatever that may be. To Maddon, assuming that people born with mutated CCR5 receptors do not need them demands a leap of faith. "We don't know that," says Maddon. "Blocking that role in a patient with HIV may not be desirable." While others, such as Doms, do not share Maddon's concerns about obstructing CCR5, they do think Progenics's data look promising. In mice engineered to harbor human immune systems, the virus became almost undetectable after treatment with the company's lead antibody, PRO 140, for four to six weeks. Progenics expects to have PRO 140 and another attachment-inhibiting antibody in clinical trials next year.

While companies may appear to be competing to create the best CCR5 inhibitor, their efforts are actually complementary. Each drug binds to the doughnut-shaped CCR5 receptor slightly differently. "Resistance to one doesn't buy you resistance to others [CCR5

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inhibitors],” adds Doms. As for its role in the HAART regimen, no one expects a CCR5 inhibitor to single-handedly suppress HIV. These compounds will only work in concert with other antiretrovirals. We must anticipate the downside, Doms cautions. “There’s going to be variability and there’s going to be resistance. It’s important to prepare ourselves. But I think they’re going to do well.”



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