# AIDS IN THE 21ST CENTURY:
## Confronting the Challenge at Home and Abroad

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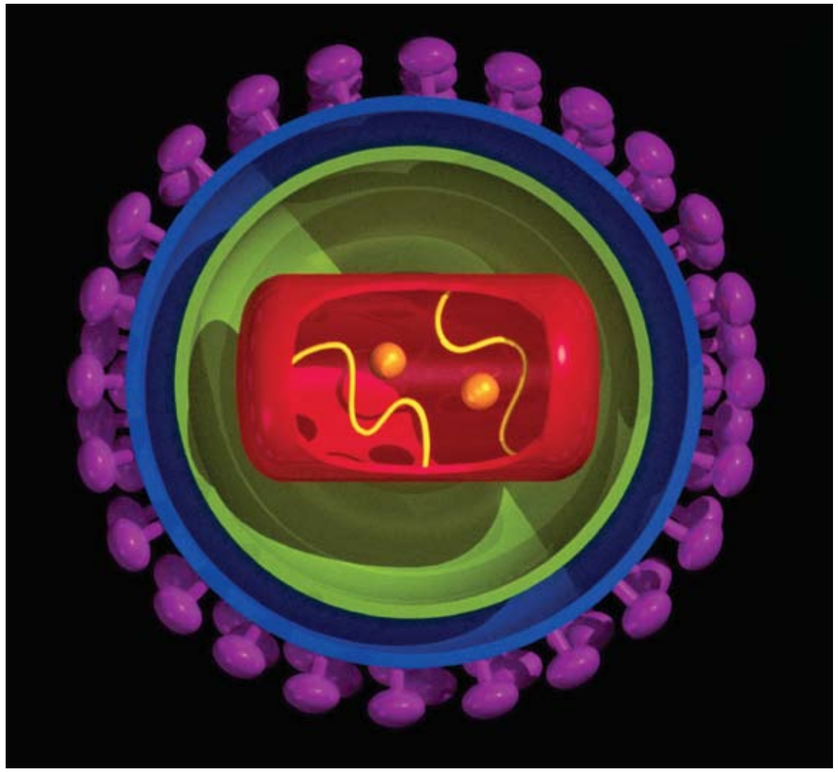
Albert Einstein College of Medicine's Center for AIDS Research (CFAR) was created in 1988 with funding from the National Institutes of Health (NIH), largely to capitalize on the College's unmatched expertise in pediatric AIDS. As the incidence of the childhood form of the disease began to wane (at least in the Western world), CFAR began to evolve, broadening its mission to address everything from delineating the molecular biology of HIV to preventing the spread of infection by understanding the behavior of substance abusers in the Bronx and sex workers in Mumbai, India. Today, under the direction of Harris Goldstein, M.D., the Center supports the work of some 60 principal investigators in seven major areas: developmental therapeutics, epidemiology, HIV-associated pathogens, immunology, substance abuse and behavioral interventions, viral pathogenesis, and international outreach. To illustrate the current scope of AIDS research at Einstein, three ongoing CFAR projects are described below: two novel methods of attacking HIV—radioimmunotherapy and prefabricated immunity—and a grassroots program for people with HIV in Rwanda, informed by lessons learned fighting the epidemic here in the Bronx.



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### A SMART BOMB AIMED AT HIV

A decade ago, highly active antiretroviral therapy, also known as HAART, revolutionized the treatment of AIDS, transforming infection with HIV from a fatal illness into a manageable chronic disease. What the next breakthrough will be is not clear, but a highly promising candidate is radioimmunotherapy, in which antibodies are used to ferry a lethal dose of radiation directly to cells infected with HIV.

Left alone, HIV infection progresses as the virus hijacks T cells—which orchestrate the body's response to intruders—and turns them into factories for making HIV. New copies of the virus are then released into the bloodstream, where they infect more T cells, steadily weakening the immune system.

HAART breaks this vicious cycle by blocking viral replication in newly infected T cells. Established T-cell infections, however, are left untouched. Thus, HAART can control HIV infection, but it cannot cure it.

"You can treat patients with antiviral drugs for years and they will have no detectable virus in the bloodstream," says Harris Goldstein, M.D., Professor of Pediatrics and Microbiology & Immunology. "But within weeks after stopping therapy, the virus comes right back because there are all these pockets of HIV-infected cells. It's like the Taliban hiding in the caves in Afghanistan. When you stop bombing, they come right out and start fighting all over again. So, the question is, can we come up with a therapy that can specifically target HIV-infected cells and eliminate those reservoirs of HIV?"

One answer may be radioimmunotherapy, or RIT, which marries the specificity of antibodies with the destructive power of radiation, in the form of a few molecules of a radioactive isotope. Because each type of antibody is specific for only one type of antigen, the radiation can be targeted with great precision, minimizing collateral damage to healthy cells. It's the medical equivalent of a smart bomb.

RIT was originally developed as a treatment for cancer. Two RITs were recently approved for treating lymphoma. Now, researchers at Einstein are trying to adapt this technology for fighting infection with HIV.

Since viruses are much different from cancer cells, the creation of a radioimmunotherapy for HIV posed significant challenges. Viruses are mere wisps of DNA or RNA wrapped in a thin protein coat. Simple, tough, and resilient, they slough off radiation like rainwater and can readily repair any damage that might occur. What's more, HIV can hole up in T cells, beyond the reach of antibodies.

"So, our approach is not to target the viral particles but rather T cells that harbor the virus," says study leader Ekaterina Dadachova, Ph.D., Associate Professor of Nuclear Medicine and Microbiology & Immunology. "The good thing is that T cells are among the most radiosensitive cells in the body."

Dr. Dadachova's immunotherapy consists of an antibody for glycoprotein 41 (gp41) and a radioactive isotope called Bismuth-213, bound together with a special molecule known as a ligand. The gp41 antibody was selected because its corresponding glycoprotein is reliably expressed on the surface of T cells infected with HIV and, unlike other HIV-related glycoproteins, it usually doesn't shed into the bloodstream. Bismuth-213 was chosen because of several characteristics, including a half-life of 46 minutes. Such a decay rate allows just enough time for the treatment to be prepared and administered and for the radioactive antibodies to do their job, but not so much time that the patient would have to be sequestered for very long. After four hours, Bismuth-213's radioactivity falls to negligible levels.

The treatment, given as an intravenous infusion, would be complemented with a dose of HAART, so as to destroy the viruses when they are flushed out of their "caves."

With so many pieces needed to make the RIT puzzle, Dr. Dadachova has had to call on the expertise of a wide variety of researchers. Her collaborators at Einstein include Arturo Casadevall, M.D., Ph.D., the Leo and Julia Forchheimer Professor of Microbiology & Immunology and Chair of the department, who is also collaborating with Dr. Dadachova on developing RITs for melanoma, fungi, and bacteria; Dr. Goldstein, who specializes in mouse models of HIV and in the pathogenesis and treatment of HIV disease; and Mahesh Patel, M.D., Assistant Professor of Medicine, a researcher in Dr. Goldstein's lab. In addition, the human monoclonal antibodies were provided by Susan Zolla-Pazner, Ph.D., an immunologist at NYU School of Medicine, the ligand by Martin Brechbiel, Ph.D., an investigator in the radiation oncology branch at the National Cancer Institute, and the isotope by Alfred Morgenstern, Ph.D., and Christos Apostolidis, Ph.D., nuclear chemists at the Institute for Transuranium Elements in Germany.

In an encouraging start, Dr. Dadachova and her colleagues, supported by a CFAR pilot project award, have demonstrated that the treatment is effective at killing T cells both *in vitro* and *in vivo*, the latter involving two different models of mice with HIV. Results of their proof-of-principle study were published in *PLoS Medicine*.

The technology has already been licensed to a commercial partner, which is working to make large quantities of clinical-grade antibodies. Clinical trials are perhaps a year or two away.

Dr. Dadachova predicts that RIT can also be developed for other infectious diseases, including those caused by antibiotic-resistant microbes. ■

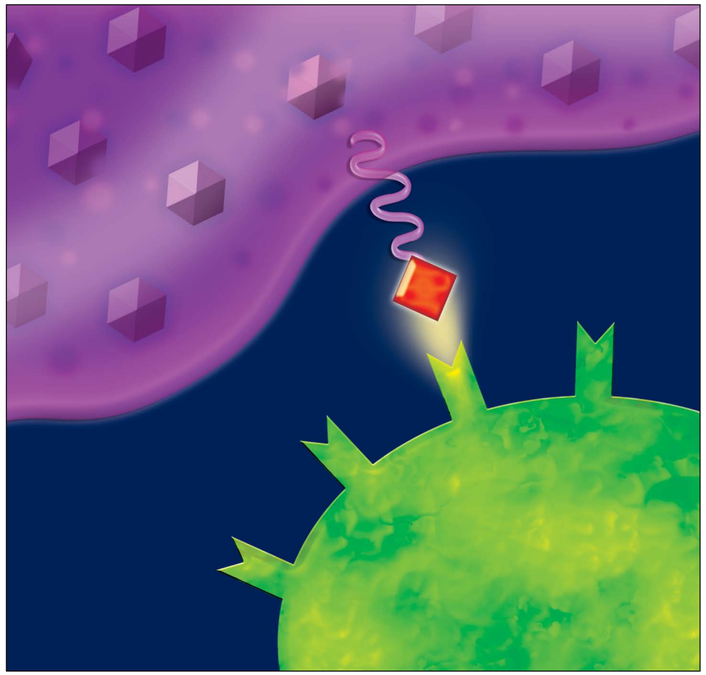
### CUSTOM-MADE IMMUNITY

One of nature's most crafty viruses, HIV is able to dodge just about everything that the immune system can throw its way. But a small percentage of people infected with HIV manage to keep the virus in check without any medications. The secret to these "elite controllers," who number about one out of 300 people with HIV, may be in having T cells that are highly efficient at eliminating cells infected with the virus.

Unfortunately, these super T cells cannot be transplanted from one patient to another. "Your own T cells would reject them, or they would attack your cells," explains Dr. Goldstein.

But the researcher may have discovered a way to get around this immunological roadblock. It appears that some T cells from elite controllers have a receptor that is particularly adept at recognizing cells infected with HIV, which express unique epitopes (antigenic fragments of the virus) on their surface. Based on that insight, Dr. Goldstein surmised that it might be possible to confer immunity to HIV by transplanting into patient's T cells the genes that code for this receptor.

The first step in creating this therapy was to clone the genes for the receptor. Next, the cloned copies



**Certain AIDS patients can keep HIV at bay without drugs. Some of their T cells have a cell-surface receptor that recognizes HIV-infected cells. Dr. Goldstein is developing an AIDS therapy to equip patients' T cells with cloned copies of the gene for the receptor. This illustration shows a T cell (lower right) with a receptor that is binding to a cell infected with HIV.**

were inserted into lentiviruses—a type of virus skilled at inserting its genetic cargo into the DNA of other cells.

At this point, the therapy, dubbed "prefabricated immunity" by Dr. Goldstein, can be applied to any patient. When the lentiviruses are incubated with T cells collected from a patient with HIV, those cells would incorporate the new receptor genes and—when infused back into the patient—be programmed to express the corresponding highly reactive HIV-specific surface receptor.

"In theory, if you give those altered T cells back to the patient, they will be armed to recognize HIV and eliminate infected cells," says Dr. Goldstein. Thus far, his group has shown that this novel therapy potently blocks HIV infection in mice.

Since the virus has a remarkable ability to mutate, the ultimate version of the therapy will transfer genes for as many as ten different HIV receptors. "This would immediately provide the recipient's immune system with the capacity to recognize ten different epitopes of HIV at exactly the same time—essentially parallel immune processing, " says Dr. Goldstein. "HIV may mutate in one direction or another, but there would still be a T cell there to recognize it."

A similar broad-spectrum approach is used in HAART, where a variety of antiretroviral drugs are thrown at HIV at once, reducing the chances that the virus will happen upon a successful mutation.

Dr. Goldstein does not imagine that prefabricated immunity will cure patients infected with HIV. But it could prove to be a life-saving immune-system boost for the 20 to 30 percent of HIV patients who don't respond well to antiretroviral medications.

The treatment might also be useful in preventing infection following acute exposures to HIV—for example, after needle-stick injuries (which are distressingly common among health-care workers) or after high-risk sex. "If you attack the virus very rapidly and eliminate it, you may prevent infection," he says.

Assuming prefabricated immunity is shown to be effective in clinical trials, Dr. Goldstein expects that it would move rapidly through the approvals process. "Our approach uses tools that have already been approved for patient use, so we wouldn't have to get approval for a whole new therapy, just a variation," he says. "Therefore, I am hopeful we are talking in terms of years as opposed to decades."

Like radioimmunotherapy, prefabricated immunity could conceivably have applications well beyond AIDS. "This is exciting because it is a completely new approach to therapy that may be effective against any viral infection," says the researcher.

Although sophisticated and costly molecular biology tools are needed to make prefabricated immunity, Dr. Goldstein believes the therapy could be adapted for use in the developing world. "In terms of the technique involved, it's very straightforward," he says. "Once the lentivirus is made, I could train you to make the therapy in about an hour. You would need an incubator, a hood, and you would have to know how to collect blood and isolate T cells."

Manufacturers, he adds, have a way of making products less and less expensive. "Ten years ago, everyone said that we couldn't afford to bring antiretroviral therapy to people in Africa because it was too expensive. Well, that was proved to be wrong." ■

## HELPING RWANDA HEAL

Even the word "incomprehensible" doesn't seem strong enough to describe the recent history of women in Rwanda.

In a hundred-day period in 1994, Rwandan soldiers and Hutu gangs slaughtered 800,000 Tutsis and moderate Hutus. A quarter-million women were raped, and tens of thousands were infected with HIV. A decade later, many of them were dying of AIDS.

The story gets worse. Before inexpensive antiretroviral therapy arrived in Rwanda in mid-2004, the drugs were given to the alleged rapists in international prisons, but not to their deathly ill victims in Rwanda.

Fortunately, this last injustice is now being rectified. In 2004, two

physicians and an activist-journalist from America teamed with a group of the survivors, Rwandan officials, and a handful of nongovernmental organizations (NGOs) to create Women's Equity to Access to Care and Treatment, or WE-ACTx, which delivers a wide range of services to women in Rwanda.

One of those physicians is Kathryn Anastos, M.D., Professor of Medicine and Epidemiology & Population Health, a specialist in ambulatory care for urban minorities with HIV. Soon after hearing the survivors' pleas for help, Dr. Anastos and WE-ACTx's two other founders—Dr. Mardge Cohen and Anne-Christine d'Adesky—traveled to Africa to see what they could do.

"The women told us, `A lot of people come, and nobody comes back,'" says Dr. Anastos. "So, we did go back. We went back really, really fast. It was too heartbreaking. Plus, I'm a doctor. I knew we could turn things around."

Back in the 1990's, she faced a similar situation in the South Bronx, one of the nation's first communities to be ravaged by HIV and one of the last to get appropriate treatment. At Bronx-Lebanon Hospital and then at Montefiore Medical Center, Dr. Anastos played a central role in building HIV clinics and services for underserved neighborhoods and, when effective drug therapy became available, reversing the course of the disease in those living with HIV.

The fact that government agencies, health-care providers, and society at large ignored this population for so long, rankles her still. "I was outraged at how my patients were described in both the lay and medical literature, as if they were perpetrators and not victims," she says. "This was especially true for the women."

> **"The more you empower women, the greater the community cohesiveness, and the greater the commmunity's ability to take care of itself."**

A self-described child of the '60s, Dr. Anastos decided early in her career to change the system from within. In 1993, while working at Bronx-Lebanon, she won a grant from the National Institutes of Health to lead the New York consortium of the Women's Interagency HIV Study (WIHS), a study of the natural history of HIV infection in women at six sites around the country. "There was no information about how to treat my patients, especially the women, and there is still little information about men of color," she explains. Thirteen years on, WIHS continues, now at Montefiore.

In Rwanda, half a world away, Dr. Anastos found a similar challenge: a large number of women with HIV living in communities with scant health-care resources. However, the WE-ACTx team was careful not to impose Western solutions on an African population, an approach that has failed numerous times in the past. Instead, the team simply asked what the women and the government wanted. Most of all, the Rwandans wanted help with getting HIV-related care and getting enough to eat. "It was a real lesson in how to prioritize," says Dr. Anastos, who directs WE-ACTx's medical activities.

At the Rwandan's behest, WE-ACTx established two comprehensive health clinics for genocide and rape survivors, widows, and orphans. Staffed by local doctors and WE-ACTx-trained nurses, the clinics now serve more than 4,000 patients. There's also a health program for children with HIV and their families, a voluntary counseling and testing program, and a nascent national cervical cancer screening program.

A variety of nonclinical projects have been started as well, including a supplemental nutrition program, small income-generating projects, a program for training HIV trainers and peer educators, and a pilot legal aid training program for paralegals and community advocates on issues related to HIV/AIDS and sexual violence. Dr. Anastos's 19-year-old daughter has also pitched in, creating a school tuition-support program for young children, linking families and communities in Rwanda with those in the United States. A total of 24 Rwandan NGOs are now involved in the organization's activities.

In addition, WE-ACTx is examining various aspects of HIV disease in Rwandan women, a sister study to the U.S.-based WIHS, funded by the National Institute of Allergy and Infectious Diseases. As with the clinical programs, the research was undertaken with enthusiastic local support. "The community drives the care," Dr. Anastos says. "Nothing that we do in Rwanda would have succeeded without the government, without the grassroots organizations or the women themselves. What we are is the facilitator."

It's a model that she hopes others will emulate. "We are not the only people saying this, but the answer to AIDS in Africa and Asia is that you have to empower women," she says. "Women hold families together. In many of these agrarian communities, they are doing most, if not all, of the field work. The more you empower women, the greater the community cohesiveness, and the greater the community's ability to take care of itself." E