Immuno’s Defense

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What is it about the human immune system that makes the most brilliant scientists, educators and writers sound like comic-book-addicted fifth-graders? When talking about the immune system response to infectious diseases like HIV, they collapse into simplistic metaphors of war and invasion, of armies and generals waging a constant battle against unknown enemies. Look no further than Elinor Levy, a noted immunologist at Boston University. In her 2003 book on the worldwide evolution of infectious diseases, The New Killer Diseases, she and coauthor Mark Fischetti write: “The human race is in the midst of an escalating biological war against an army of microscopic foes.” But Levy is hardly alone. Even the National Institutes of Health (NIH), our nation’s largest source of funding for medical research, titles one of its online fact sheets “Our Immune Army.”

It’s true that such analogies help explain the pernicious effects of the virus to a wide-eyed public. HIVer Cathy Olufs, a treatment activist and educator who was diagnosed in 1995 and works with incarcerated HIVers in the LosAngeles area uses just these kinds of metaphors when helping clients understand, say, the importance of adherence in battling—whoops!—resistance. But she wonders whether oversimplifying how newly diagnosed HIVers view the immune system also leaves them unprepared to analyze both the value and the shortcomings of HAART.

Aware of her own knowledge gaps, Olufs recognizes that the immune system is far more complex than the way she talks about it with inmates. “I didn’t go to school for 15 years to be a researcher like some of the doctors did,” she says. But she worries that some researchers she encounters in her treatment activism have an equally unsophisticated view of the immune system. Indeed, the immune system more closely resembles a vast, interconnected network of societies learning to get along with one another than a cellular game of war. And though some immune cells do hunt down unwelcome bacteria and viruses, one thing that makes the immune system so awe-inspiring is that it can learn to coexist peaceably with these creatures, too.

Although our understanding of the immune system has deepened substantially, key scientific questions about HIV remain. Chiefly: How does HIV cause most CD4 cells to eventually die off, leaving the immune system virtually defenseless against the opportunistic infections responsible for most HIV deaths? Answering this question has become the grail of immune-based research, and it is increasingly obvious that doing so will require that we fundamentally change how most people think about the immune system and what a cure for HIV might actually look like.

To Olufs, this challenge is exhilarating. “The immune system is like a totally new frontier that hasn’t been completely explored,” she says. “There’s a lot of hope about finding treatments that actually work with it.” In fact, some of the most cutting-edge research on the immune system’s response to infection suggests that a cure for HIV won’t mean eradicating the virus with drugs as much as teaching the immune system how to safely tolerate it.

But few HIV scientists and policy makers share Olufs’ hope. On the whole, researchers have focused almost exclusively on the virus, not the immune system, displaying a notable lack of imagination about its potential to become the focus of future treatment breakthroughs. Indeed, the current generation of antiretrovirals (ARVs)—despite the technological marvels that brought them to life—are one-shot wonders compared to the vast repertoire of immune cells. Indeed, HAART owes most of its HIV-slaying success to the immune system’s underlying health. When the immune system is broken beyond repair, HAART is crippled too. That’s why HIVers are urged to start HAART well before their CD4 cells drop below 200. Swooping in, like the proverbial superhero, after HAART begins to fail is just one way that immune-based therapies (IBTs) could save the day.

Given HAART’s limitations, any reasonable person would assume that both the government and industry are working overtime to develop new kinds of medication that enhance the body’s own defenses. But this is far from the case. Stymied by failed attempts to produce a clear IBT blockbuster, an uncertain path to getting an IBT approved and a shrinking pool of money, both the government and the pharmaceutical industry are playing it safe, lavishing the bulk of their remaining dollars on improving HAART. This tunnel vision angers top treatment activist Martin Delaney, who says, “We’re not gonna cure the disease till we get to correcting the problem of the immune response. We need some shit kickers out there, somebody questioning the conventional wisdom.”

Sign Olufs up. “There ain’t a lot of hope left that we’ll find some miracle antiviral that’s going to cure HIV,” she says. And despite our best efforts, it will likely take HIV meds that are a lot better—and far cheaper—than current meds to save the lives of the 38 million HIVers living in countries less wealthy than our own. At the very moment when IBTs hold the best hope for a sustained defense against—and possibly a cure for—HIV, these therapies face their greatest obstacles. But there is still a chance to inject IBT activism and research with renewed energy and support. But it will mean changing the minds of those who fail to see beyond the glitter of ARVs. Call it Immuno’s Defense.

Under a Microscope

Granted, the most radical IBT approaches are farther away than the next crop of anti-viral drugs, CCR5 antagonists, which have hogged the headlines. But new approaches to older drugs like IL-2, hydroxyurea (HU) and human growth hormone (HGH)—all of which had been declared dead—have been resurrected and deserve some publicity. The field of study called pathogenesis, explaining how HIV causes disease progression, now offers overwhelming evidence that while HIV does infect and kill important immune-system cells, the virus alone is not responsible for the destruction that causes illness and death. Researchers now agree that the immune system’s failure to fight HIV is, paradoxically, caused by a response that is far too aggressive, rather than too weak.

Franco Lori, MD, a scientist at the Research Institute for Genetic and Human Therapy in Washington, DC, and Pavia, Italy, describes how a too-active immune system is actually harmful in the face of HIV: “It’s fine for the immune system to respond aggressively to HIV. It’s not OK when this happens for years. If you look at a car engine, used properly it can last for a long time. But if you’re always going too fast in low gear, the engine is going to burn out.”

A research agenda that prioritizes treatments to quiet this overly aggressive immune response could ultimately lead to new means of not only treatment but prevention. Getting government and pharma to invest in this new research agenda won’t be easy. Bob Huff, editor of GMHC’s Treatment Issues, says prevailing attitudes about HIV “can shape research agendas [as well as political agendas] for years.” And while the virology-dominated establishment accepts the key role our immune systems play in controlling HIV, the bulk of government and industry dollars remain planted in HAART.

The contribution of HAART to thehealth and survival of HIVers is unassailable. But Delaney says that when he tries to get scientists interested in IBTs, pointing to HAART’s limitations—including their long-term side effects and vulnerability to resistance—the response is beyond disappointing. “At every scientific meeting, I make a stink about the lack of interest in IBT research,” he notes, “but the virologists say, ‘We tried that and it didn’t work, and the antivirals do work, so stop telling us what to do!’ ”

But not all virologists think alike. Joseph Gathe, MD, an HIV doctor and clinical researcher from Houston, readily concedes that HIV meds are not the only answer. In a publication commemorating the 10th anniversary of HAART, Gathe said, “HAART has delivered time, but it has not delivered a cure.”

Delaney doesn’t just blame the virologists, saying, “[Activists also] make idiotic statements, like ‘The problem of HIV disease has basically been solved except for access issues,’ as though it’s OK that everybody is on lifelong therapy that costs $20K a year. Yes, it’s better than being dead, but it’s not a solution.”

Of course, HAART can have a positive impact in the immune system. When it works, it readily quiets down the immune response: With fewer copies of virus around to taunt immune cells, the system backs off. This provides the breathing room for the immune system to recover significantly. But for those HIVers who suffered extensive immune damage before HAART arrived, a favorable immune response to treatment is not at all certain.

Consider Matt Sharp, a veteran activist who works with Test Positive Aware Network in Chicago. Sharp did well on a salvage regimen for quite a while, but the treatment never got his CD4 count over 200. Sharp says, “My viral load has stabilized in the last couple of years—at around 15,000 to 20,000—which for me is low. [But] recently, my CD4 count dropped below 100 for the first time in about five years. Also, I still have a lot of skin problems and get bacterial pneumonia almost every winter.”

What Sharp and the growing numbers of HIVers who are running out of our limited antiviral arsenal need are new treatments that provoke the immune system into rebuilding itself without stimulating it so much that newly gained cells are immediately infected or destroyed.

IL-2: An Old Dog Learns New Tricks

In the early ’80s, before HIV was even discovered, researchers figured that if HIV disease smoked CD4 cells, perhaps IL-2—one of the immune system’s messenger boys—could resurrect them. Michael Lederman, MD, a professor of Medicine at Case Western Reserve University in Cleveland, says, “When IL-2 was first tested in HIV, we didn’t have HAART to keep virus suppressed. Studies showed that IL-2 could dramatically increase CD4 cells. Since [we believed then]that the number of CD4s is the best predictor of clinical outcome, this approach was greeted with a great deal of enthusiasm.”

Unfortunately, IL-2 was initially given at high doses without HAART. Between the awful side effects and out-of-control virus replication, the early studies likely did more harm than good. Still, some activists and researchers never gave up on it, and into the ’90s, a number of clinical trials were launched to determine a safe dose that would still boost CD4s. But IL-2 doesn’t just cause the body to churn out new CD4 cells; it also causes HIV to multiply astronomically. Until we had drugs that could keep viral load in check, researchers were afraid to use it. Now, IL-2 is undergoing two large international studies charting whether it increases health and survival over and above the effects of HAART.

In understanding the IL-2 approach, it’s crucial to realize that CD4 cells are not all alike. So-called naive CD4s, for instance, can respond to any number of infectious critters. For people who’ve lost their naive CD4s, restoring them is the key to renewed health. Skeptics didn’t think IL-2 would be capable of increasing fully functioning naïve CD4 cells. A newly published study by researchers at the NIH found that naive CD4s generated by the body in response to IL-2 had a lifespan about nine times longer than naive CD4 cells in people not treated with IL-2. The study’s lead author, Joseph Kovacs, MD, contends that we will have to evaluate IL-2’s benefits differently from HAART’s. He writes that rather than looking for short-term gains, we’ll have to be patient, as “IL-2’s effects on HIV disease progression may become apparent only in long-term follow-up.”

HU: The Come Back Kid

Another drug whose fortunes have waxed and waned is hydroxyurea (HU), an FDA-approved drug for pancreatic cancer originally studied as a way to make a particular HIV med work better. The darling of researchers in the late ’90s, HU was dealt a final blow in 2004 when the U.S. treatment guidelines panel voted that it should never be used. But Lori, one of HU’s pioneers, calls that a bum rap, pointing to new research indicating that it may be useful as a suppressor of immune over-activation.

Lori says, “In the latest studies, we found that the lowest dose of HU was not only the least toxic, but also the most effective. This was unexpected, because with a typical drug you usually expect the highest dose to work most effectively.” Delaney agrees with Lori’s characterization: “A whole string of drugs that ought to be looked at have had ice water thrown on them by researchers at

the AIDS Clinical Trials Group [ACTG] and many activists as well. They all lead with the argument: 'HU was bad. It caused toxicity.' I say 'Compared to what'? What [HIV med] doesn't produce toxicity?'" Furthermore, some researchers say the toxic side effects experienced by some HIVers taking the HU were more likely caused by the [HIV med] it was paired with. The important remaining question is not whether to use it, but how to use it."

HGH: More Than Muscle

HGH was the rage when HAART arrived. Since HIV-related wasting was rampant, any therapy that could reverse wasting and confer a survival advantage was prioritized. For researchers and HIVers alike, HGH best met that promise. But its price and appeal to the bodybuilding circuit made it a black-market commodity and ripe for counterfeiters, which caused it to become a drug non grata for most insurers and AIDS Drug Assistance Programs. When HAART proved to be as effective at reversing wasting as HGH, most researchers felt it no longer merited much attention.

However, researchers like Mike McCune, of UC San Francisco's Gladstone Institute of Virology, thought that hints of HGH's ability to prod the thymus into action might be meaningful. And recognizing the limited ability of HAART to restore immune function, McCune believed the thymus was of vital importance. He and his colleagues produced several studies throughout the late '90s, that showed that for people whose immune systems don't recover significantly while on HAART, stimulating the thymus could be the best solution.

At last summer's International AIDS Society Conference in Rio De Janeiro, Kimberly Smith, MD, of Rush University Medical Center presented a study where HGH increased the size and function of the thymus and boosted CD4 cells in people who had never attained immune reconstitution despite having been stabilized on HAART. Even Smith, the lead investigator, was cautious when speaking to reporters at the conference, however, saying, "It's too early to change clinical practice. We have to show that this improvement in cells is meaningful."

Few activists expect any of these "old dogs" to become the powerful new IBTs that HIVers are awaiting. But such treatments may provide significant added value to HAART in people with failing regimens—buying them the time they may need until IBT research hits its stride. They also provide the kind of data on immune function that help scientists figure out what else needs to be studied.

Sharp has been prompted to try IL-2 recently to deal with his falling CD4 count. And though he's not thrilled about enduring flulike symptoms for the five days of injections he'll receive every month, he says, "After everything I've survived so far, I can get through a week of IL-2 side effects. Knowing that keeps me going."

Sharp's fellow activist and long-term HIVer Nelson Vergel also finds himself willing to give IBTs another chance. "I have 40 T cells. I've been positive for 22 years, and for people like me and my friends, [IBTs] don't usually seem like something that will arrive in time to help us,we tend to think short-term: what's going to help me in the next three years, " says Vergel, whose last antiviral salvage combination failed. But he adds: "When I heard about a new [IBT] study using genetically

modified CD4 cells, for the first time in years I was like, 'Yeah, I want to join.'" Unfortunately, the California study is too far from home for Vergel, to participate in, but he is encouraged by IBT studies finally appearing that appeal to him and others with few HAART options left.

A Shot in the Dark

Despite the challenges confronted by IBT researchers, there are a number of "next generation" treatments currently being studied. These include attempts to manipulate the immune system's communication network through the use of cytokines like IL-7, which also causes the thymus to produce new cells. New research into immune-suppressive drugs like cyclosporine is in the beginning stages, and gene therapy is finally getting off the ground after almost three years of safety-related delays. Lastly, researchers also have renewed optimism about therapeutic vaccines.

Getting vaccinated for a disease like HIV usually involves injecting our bodies with something that resembles the virus, teaching the immune system to respond quickly if it ever encounters the real thing. A therapeutic vaccine is designed to encourage the same kind of immune response, but rather than prevent infection with HIV, the vaccination is intended to improve the immune response to the virus in someone who's already infected. A number of companies and researchers have tried this approach in the past and failed to show any benefit at all.

But this past year, French researcher Jean-Marie Andrieu, MD, took therapeutic vaccines in a new direction. Rather than inject a person with HIV, he decided to take a person's virus and some immune cells out of their bloodstream, teach the cells how to respond to the virus in test tubes, and then give the newly schooled immune cells back to the person he took them from. This resulted in one of the first successful therapeutic HIV-vaccine studies. Lederman was impressed by the "startling results" of the trial. Of the 18 HIVers given these primed immune cells, eight had a sustained reduction in viral load and stable CD4 counts a year after the vaccination. The other participants also had an initial drop in virus, though that was lost over time.

Any company hoping to market a new treatment for HIV must prove that it's safe and will work as promised. Daniel Raymond says, "Antiretroviral therapy has an advantage over IBTs—you can get a new [HIV med] approved based on surrogate markers [like CD4 count and viral load], rather than on clinical endpoints [like survival], so it takes less time and less people to do those studies. Until there's an IBT approved for HIV, it will seem too risky for companies to invest resources in developing something."

Cathy Olufs puts it more bluntly: "There's no instant gratification with IBTs. Pharmaceutical companies probably see IBTs as a money pit. But for me—and most other people with HIV—it's a pit worth falling into."

Financial risk isn't the only hindrance. The NIH has funded research where the return on investment is dicey but the need among people with a particular disease is great. And the branch of the NIH that tests therapies for HIV in people, the ACTG, does have clinical trials of several immune-based therapies enrolling or set to begin. But those 10 or so trials likely to happen in the next year can't compete with dozens of HAART trials sponsored by the NIH or dozens more

sponsored by pharmaceutical companies.

A Rocky Road for IBTs

Delaney, meanwhile, feels that many leading AIDS researchers are too close to the pharmaceutical industry to seriously explore IBTs: "[They're] on advisory boards; they're the featured speakers on symposiums run by the companies." But if most HIV researchers aren't influenced by their proximity to pharma, the majority are more likely to have backgrounds in virology and infectious diseases than in immunology—and this alone influences how they think about solving problems. Stanford researcher Jay Levy, MD, says, "I'm a trained virologist. My work in the beginning was to identify virus, how it acts.... Then [my colleagues and I] realized that for long-term survivors it didn't matter what was going on with the virus—their increased survival was dependent on factors associated with the immune system, so I shifted focus to the immune system.... Is that popular? No—because the immune system is quite complicated."

Such complexity makes IBTs difficult to sell not only to pharmaceutical companies and government researchers, but to HIVers and community activists. It doesn't help that most HIVers are told by their doctors how manageable HIV is and how likely they are to "live out a normal life span." It's striking that even though no one has been on HAART for more than 10 years—hardly a normal life span—researchers feel confident about its life-extending capacity. Optimism and hope are vital forces, motoring HIVers through the roughest of times, but is there a price to letting all our dreams for the future rest on ARVs?

Daring to Dream

In 1992, very little of the AIDS research being conducted, IBT or otherwise, was focused on people with fewer than 50 CD4 cells. It took a smart, stubborn, opinionated HIVer and activist named Jesse Dobson, to turn this around. Dobson's stubbornness was matched by his fascination with science, and with the support of Project Inform, he brought together what were then the world's top HIV researchers to confront this problem. That first meeting, dubbed the Immune Restoration Think Tank (IRTT), began with a demand that the researchers leave their egos at the door and Dobson asking each of them what to him was the most important question of all: "Did they believe it was possible to restore a broken immune system?" The researchers at that first IRTT meeting, and all subsequent meetings, answered yes.

Dobson died a year after the first IRTT, and though times and treatments have changed dramatically since then, the fundamental question he posed to the first group of IRTT researchers is still relevant. "Do we still believe it's possible to heal a broken immune system?" But perhaps, in 2005, we must add: "Can it happen sooner rather than later?" For those struggling with the debilitating burdens of life with HIV, it may seem grotesque to suggest we dream of a cure for AIDS and look with awe to the immune system, which has failed them so spectacularly, as the source of that cure. But HIVers and researchers alike must be willing to dream and imagine.

Comic books, with their cardboard heroes and villains, may seem fantastical, but they embody the spirit of imagination that drives writers and artists to tell stories and young men and women to wait breathlessly for the next installment. Some of yesterday's most loyal and wide-eyed comic-

book fans may be the activists and researchers that blast us into the future of HIV treatment.

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