It Takes IL-2 To Tango

This hot treatment raises questions but provides one answer: Scientists shut each other out at their own peril

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Even though CD4 count has had its day in the sun as a predictor of HIV diseaseprogression, the summer's hot new treatment gossip buzzed around a promising therapycalled IL-2 -- whose main effect is to boost CD4 count to sometimes phenomenal heights.Too good to be true? It may be. But the real news is that a scientific turf battlemay have kept this therapy out of reach for several years longer than necessary.

It sounded like the miracle for which everyone had been praying: A new treatment was revving up the immune system and increasing CD4 cell production by the hundreds. The CD4 cell counts of men and women infused with the immune system protein interleukin-2 (or IL-2) rose more than 50 percent over the course of a single year. One man watched his counts almost quadruple. The counts of two others had stayed above 1,000 for almost three years.

The formal research findings announced in March by a team from the National Institute of Allergy and Infectious Diseases (NIAID) confirmed the rumors that had been sweeping across the country about women whose CD4 cells had doubled in three weeks and men whose CD4 counts had reached 3,500, thanks to a drug used originally to treat metastatic kidney cancer. Patients who found access to the drug -- either through clinical trials or by persuading their physicians to prescribe it "off-label" -- had become IL-2 crusaders, preaching conversion from antiretroviral therapy to immune modulation. Suddenly electronic bulletin boards were alive with discussions of how to convince wary doctors to prescribe IL-2, how to mix it at home and how to endure its often-severe side effects. The National Institutes of Health (NIH) and Chiron, manufacturer of Proleukin (the brand of IL-2 used in the studies), announced new trials to test new dosages and new dosing regimens. Dr. Larry Bruni of Washington, D.C. was one of the first community physicians to jump on the IL-2 bandwagon. The demand became so great that after Blue Cross cut him off as a provider, he was still swamped with patients so desperate to try IL-2 that they were willing to shell out cash -- at $2,400 a course of treatment.

But as IL-2 becomes the nation's latest popular unproved treatment for people with asymptomatic HIV disease, many physicians worry that patients with CD4 counts below 100 -- the ones most likely to be harmed by a drug that promotes the growth of HIV as well as of CD4 cells -- will begin taking it. Members of Treatment Action Group (TAG) are furious that some community physicians such as Bruni have begun to use IL-2's ability to raise CD4 cells as "an attractive marketing tool

for their own practices: ’Come see me and watch me raise your T-cells,’” says TAG’s Gregg Gonsalves. Bruni’s hype, appearing in his advertisements (including in *POZ*), converted the experimental therapy into the Wonder Drug. The hype became so optimistic that Gonsalves wants NIAID director Dr. Anthony Fauci to issue an official clinical alert to doctors warning that “we do not know the long-term clinical effects of IL-2 therapy, that IL-2 up-regulates HIV and has its own extreme toxicities.” (According to a September exposé by Bill Gifford in the *Washington City Paper*, Bruni has other problems, including a 1994 bankruptcy filing and a $4.1 million jury verdict against him and two co-defendants last June in a civil case brought by a former Catholic priest whom Bruni treated for HIV for years; the priest turned out to be HIV negative.)

And savvy treatment activists on both coasts are voicing skepticism about a treatment regimen that raises more questions than answers: What do the CD4 cell increases really mean? Are 1,000 IL-2-induced CD4 cells the same as 1,000 naturally induced CD4 cells? Are the new CD4 cells functional? Is IL-2 simply forcing the body to churn out cells that will turn out to be virus chow? Is it really safe to infuse patients with the very drug used to grow HIV in the laboratory?

They aren’t getting many answers. Although IL-2 research for AIDS predates the discovery of HIV, scientists are still stumped by many of these basic, critical questions. The virology-fixated AIDS research establishment is woefully bereft both of an understanding of how HIV damages human immune systems and of tools for developing such an understanding -- the legacy of a federal AIDS research program so focused on the “it’s the virus, stupid” principle that scientists, physicians and patients are unprepared to deal with any therapy with an immunologic basis.

That’s hardly surprising given the stranglehold virologists established over most of AIDS research in the early 1980s. Dr. Nancy Klimas of the University of Miami began to understand that reality at her first meeting of Veterans Administration AIDS researchers in 1986. A young immunologist, she was anxious to apply her newly developed skills to the new disease, but her enlistment in the war against AIDS was hardly greeted with hurrahs. Instead, a senior researcher dismissed her fliply: “Immunologists have no role to play in AIDS.” Klimas was stunned. Sure, a virus was involved, but the disease was destroying CD4 cells and deregulating immune systems. How could immunology be irrelevant?

It never has been, but that has not stopped the official AIDS research establishment from putting virtually all of its eggs into the virology basket and ignoring treatments designed to bolster the immune system rather than murder the virus. As Klimas begged for funds to devise ways to rebuild decimated immune systems, she watched while her Miami colleague, Dr. Margaret Fischl, pulled in millions of dollars in major grants from the federal government and pharmaceutical companies to test drugs that might kill, or at least slow, the virus. Her experience became the plaint of immunologists across the country.

After all, immune manipulation wasn’t as sexy as a magic HIV-killing bullet.

Frustrated by the overconcentration on the search for such weaponry -- which, even if the elusive magic bullet were found, would still leave physicians clueless as to how to rebuild permanently

damaged immune systems -- West Coast activists, lead by Martin Delaney and Jesse Dobson of Project Inform, organized their own immune reconstitution think tanks. These have evolved into regular seminars on whether immune systems can recover from HIV infection -- and to foster cooperation among scientists interested in figuring out how to do so. While federally funded scientists poured millions of dollars into testing and retesting AZT and its cousin drugs -- ddI, ddC and d4T -- Project Inform pushed research into the basic science of immunology, immune-boosting drugs and the transplantation of healthy immune cells.

Then came the International AIDS Conference in Berlin and the watershed year of 1993. The simple -- some might say simplistic -- model of HIV as Pac-man coursing through the bloodstream, gobbling up CD4 cells left and right until the body was left depleted of all defense, was collapsing. Senior researchers were beginning to talk seriously that HIV's most dangerous trick may be deregulating the immune system rather than murdering CD4 cells directly. But still there was no consensus as to whether the virus forces uninfected cells to merge with infected ones, whether HIV proteins cause infected cells to commit mass suicide, whether HIV simply turns CD4 cells off or whether HIV fools killer CD8 cells into destroying uninfected cells.

What little consensus there was surrounded the success of the multibillion dollar charge to locate the magic bullet against HIV: It was widely acknowledged to be a dismal failure. Dr. David Ho of New York City's Aaron Diamond Lab admitted to the press that researchers had hit a "biological wall." Early in the epidemic "scientists went for the home run: A cure, a treatment or a vaccine," he said. "But now we realize we haven't even made it to first base." Even virologist Dr. Robert Gallo, former chief of the Laboratory of Tumor Cell Biology at the National Cancer Institute and a longtime advocate of hitting HIV with a Mack truck of drugs, told delegates to forget antiretrovirals and get on with more promising strategies.

In other words, maybe it's time to look beyond virology.

For the team led by NIAID director Dr. Anthony Fauci, himself an immunologist, that meant looking for ways to guide the body's immune system to contain HIV rather than for ways to kill the virus. His approach was to manipulate the body's cytokines -- a network of proteins that serve as chemical messengers of the immune system. In HIV disease the balance of cytokines is thrown awry. Some cytokines, like tumor necrosis factor-alpha (TNF-alpha) and interleukin-6 (IL-6) are overproduced -- which apparently stimulates and perpetuates replication of HIV. Others, like IL-2, are underproduced -- which seemingly contributes to the depletion of both CD4 and CD8 cells.

Re-regulation of cytokines became Fauci's strategy for containing HIV.

Fauci's cytokine of choice was IL-2, which stimulates production of both CD4 cells and CD8 suppressor cells, which many believe to be the body's most potent weapon for containing HIV. In HIV infection, CD4 cells seem to lose their capacity to produce IL-2, and even to respond to the cytokine's signals. Without sufficient IL-2, CD8 cells aren't activated to fight HIV. CD4 production diminishes. Programmed cell death begins.

IL-2 therapy was hardly a new approach. Dr. Clifford Lane of NIAID's Laboratory of

Immunoregulation had started experimenting with it even before the discovery of HIV. Lane had no idea what was causing the immune destruction that was AIDS, but he set his sights on replacing the cells being destroyed in order to stop the disease. In the test tube, at least, IL-2, which was originally called T-Cell Growth Factor, did just that.

There were, however, two major problems. At the initial doses both Lane and oncologists testing the cytokine against cancer were using, IL-2 proved incredibly toxic. Patients suffered from high fevers, lung congestion and swelling, capillary leakage and skin problems. They experienced liver, kidney and gall bladder disorders, low neutrophils and platelets, hypotension and glucose intolerance. When produced naturally, IL-2 is secreted in tiny concentrations at specific locations by specific cells. Human bodies simply aren't designed to cope with the large quantities of the cytokine dumped into the bloodstream by infusions.

Even more frightening, once HIV had been isolated, was the discovery that IL-2 is a powerful activator of the virus. In fact, it was the addition of IL-2 to HIV-infected cells that allowed bench scientists to grow HIV in their laboratories.

Nonetheless, Lane persisted -- with discouraging results. When he infused patients continuously with the cytokine, its positive impact disappeared within weeks. Finally, he and his colleague Joseph Kovacs tried a cyclical regimen keyed to the cycles during which cells develop and mature. They admitted study volunteers to the hospital, hooked them up to infusion pumps and gave them 6 to 18 million international units of IL-2 a day for five days, then allowed the patients -- and their immune systems -- to rest for eight weeks. Six of the 10 volunteers in the trial who began treatment with more than 200 CD4 cells saw their counts increase more than 50 percent. Three had 300-to-400 percent increases. Lane had managed to keep the CD4 cells of three patients above 1,000 for almost three years with five-day booster infusions whenever their counts fell below 1,000.

These were the success stories everyone started talking about this spring. And NIAID, which had been losing its hegemony over AIDS research for two years, promoted it to the hilt. "Although current anti-HIV drugs have transient benefits, especially for individuals in late-stage disease, they do not prevent the immunologic deterioration associated with HIV disease," said Lane. "It is increasingly evident that preservation and restoration of the immune systems of HIV-infected people are necessary if they are to live for long periods of time. This study shows that IL-2 may help accomplish this."

Fauci practically gushed. "This work is a model of NIAID's 'bench to bedside' philosophy of research. In this instance, the recirculation of information from the laboratory bench to the patient's bedside, over a period of 13 years, has led to unprecedented results."

No one wanted to focus on the less-successful patients. Four of the 10 early volunteers did not respond or simply maintained their counts. No one knows why. One of the nonresponders came down with PCP several months after quitting IL-2 therapy; his count was stable at 400 cells. Lane insisted that PCP was not unheard of in HIV positive people with such high CD4 cells, but many

scientists and patients worried that IL-2 had maintained the patient's count with non-functional CD4 cells.

More troubling was that the treatment caused an initial burst of virus production -- up to a sixfold increase. That was hardly surprising since HIV's favorite targets for infection and replication are the same activated CD4 cells promoted by IL-2. With strong antiretroviral therapy such as AZT, ddI or ddC, volunteers with higher CD4s to start with managed to fight off the viral increase. But the picture was alarmingly different for those who began with CD4 counts below 200. Only two of six patients who began treatment with CD4 counts between 100 and 200 had significant CD4 increases. None of the six patients with counts below 100 enjoyed any benefit. In fact, most of the study participants with low CD4 counts couldn't fight off the increase in virus; the effect of IL-2 was a lasting rise in the HIV levels in their blood.

Physicians looked at Lane's and Kovacs' results and wondered if it was worth using the new regimen at all. It was clearly too dangerous to give the drug to the patients most in need of a new weapon. And they wondered if it was smart to subject healthy patients with 400 and 600 CD4 cells to a treatment that promised to give them rashes, fevers, low blood pressure, diarrhea, flu-like symptoms and a wide range of laboratory abnormalities including reduced calcium, albumin and magnesium without any evidence that the increases in CD4 count correlated in any way to greater health or prolonged life.

Dr. William Paul, head of federal AIDS research, put it bluntly: "While extremely provocative, it remains to be shown that this will translate into resistance to opportunistic infections or prolongation of life."

Such skepticism infuriated patients shopping for new treatments. Few denied the severity of the toxicities of the infusions used by Lane, but many believed the increase in CD4 cells were worth the misery -- or insisted that newer regimens, especially ones allowing patients to inject themselves with IL-2 at home, made the risks minimal. They didn't want to hear a lot of scientific double-talk that might take the edge off their hope.

Byron Graham of Washington, D.C. had tried AZT and given up when it made him sick. He'd been on ddI for three years but put most of his faith in a healthy lifestyle. No white bread or sugar has passed though his system for five years. He keeps his stress low and teaches yoga. Still, last fall his CD4s fell below 200 and he began to look into IL-2. "The day after the study results were released the naysayers were out in full force," Graham said. He read their arguments on a computer bulletin board and suddenly felt himself get sicker. He injected himself with IL-2 subcutaneously for four and a half days and simply stopped reading the chat group on which they posted their concerns.

But ignoring the skeptics won't change the reality that IL-2 is a therapy thriving without any proof of effectiveness -- and with clear proof of significant, and potentially dangerous, side effects. Increases in the cytokine TNF-alpha, believed to be responsible for most of IL-2's toxicity, can further deregulate the immune system and can damage the thymus gland. The jump in viral load,

controlled by antiretrovirals in patients with higher CD4 counts, can become permanent should resistance to those drugs develop.

And increasing IL-2 levels might, in fact, be counteracting an intelligent immune response to HIV infection. Some scientists believe that the best way to combat HIV is not to increase but to eliminate activated CD4 cells, which are believed to be the main site of HIV production. The underexpression of IL-2 in the bodies of HIV-infected individuals, according to this theory, might then be the immune system's way of depriving the virus of the chow it uses to replicate.

Even if IL-2 therapy is safe, its effectiveness remains open to question because more does not necessarily equal better, even in CD4 cells. Lane himself acknowledges that "the question is whether these new T-cells are good at fighting infection." Arthur Gottlieb, chairman of the department of microbiology and immunology at Tulane University School of Medicine, explained the dilemma: "Excessive emphasis [is] paid to CD4 cell numbers as opposed to CD4 cell function. The latter is the really critical issue determining a patient's course. Of course, CD4 cells decline in number over the course of HIV disease, but every CD4 cell is not equal to every other CD4 cell."

Theoretically, Dr. Nancy Klimas explains, IL-2 induces the body to produce entirely new sets of naïve CD4 cells -- CD4 cells that haven't yet learned where they should go or how to do their jobs. No one is sure how long it takes for naïve cells to learn or whether IL-2-induced CD4 cells can learn as well as naturally produced ones. What they cannot learn is immune tricks the body has already forgotten, and in HIV disease, the body gradually develops holes in its immunologic repertoire. Even people with relatively high CD4 counts have such gaps, and IL-2 cannot increase the types of CD4 cells that are no longer there. If the body has already "forgotten" how to fight PCP or CMV, IL-2 isn't going to reteach it.

So physicians know that an IL-2-induced CD4 cell increase from 200 to 1,200 doesn't necessarily put a person out of the range of opportunistic infections. Both Lane and Dr. Gwen Fyfe of Chiron worry that once IL-2 treatment has begun, CD4 count and its rate of decline will become meaningless measures by which to make decisions about the initiation of prophylaxis.

Many HIV positive people are willing to take the chance that IL-2 might not be so miraculous and are avoiding the toxicities by using a lower dose given by subcutaneous -- under the skin -- injection. But low-dose IL-2 (defined as between 36,000 units twice weekly and 3.6 million units per square meter of body surface daily) is, in essence, a different drug than the high-dose cytokine described by Lane and Kovacs. It binds to a different set of immune cells and is used to produce decidedly different results. While high-dose IL-2 is meant to increase CD4 cell counts, low-dose IL-2 targets natural killer cells in order to improve their functioning -- something the high-dose version seems unable to accomplish. Dr. Larry Bruni began playing with low-dose subcutaneous IL-2 almost five years ago and was not impressed with the results. He now uses it only for maintenance therapy. Other physicians, however -- particularly Dr. Hedy Teppler of Philadelphia -- believe that the relatively nontoxic therapy is a promising adjunct to antiretrovirals.

Teppler's patient Jonathan Lax probably has more experience with low-dose subcutaneous IL-2

than anyone in the nation: He has used as little as one-half and as much as four million units, on and off, since March 1993. The rise in his CD4 count has never been as dramatic as those in Lane's patients -- the first round they rose from 350 to 540 -- and the increase hasn't lasted more than eight months. Two years after he began therapy, his counts are down to 220, but Lax remains a believer.

"I'm convinced IL-2 works best right after you switch antiretrovirals. For those running out of efficacy on antiretrovirals, it is only marginally effective. IL-2 is a bit of a pact with the devil: You get an increase in CD4 cells, but you also get an increase in viral production. Sometimes you wonder, is this doing me good or doing me harm."

Lax has been waiting for scientists to answer that and dozens of other immunologic questions for years. When Fauci hyped IL-2 and immune therapies in Berlin in 1993, Lax sat in the audience and wondered, "Where's he been? Why didn't he push AIDS research this way from the beginning?"

Lax provides his own answer. "Infectious-disease doctors and virologists grabbed this disease with their 'kill the germ' model. Only after Berlin did the immunomodulatory approach come to the fore, the idea of supporting the host. And even then, they've never sought out people like Hedy Teppler who've been using this approach for years."

They still aren't. The Department of Immunology and Microbiology at the University of Miami recently invited a prominent outside virologist to speak at an AIDS workshop during a planning retreat. After speaking about therapies to expand CD8 cells, he argued that immunomodulation had no role to play in HIV disease treatment.

How could that be, Nancy Klimas and others argued? Expanding CD8 cells is immunomodulation, after all. No, the virologist insisted, it's antiviral therapy.

"The politics have become a question of semantics," Klimas says, still astonished at the virologic expropriation of an immunologic trick.

For people with AIDS, that question of semantics can be a matter of life and death. Despite the change in climate after Berlin -- and the efforts of activists on both coasts -- the federal AIDS research establishment remains dominated by virologists who now seem to be teaching themselves immunology rather than turning the reins of power -- and the federal research dollars -- over to their colleagues.

No one can calculate how many will die before they master Immunology 101.
