Vintage Gallo

The visionary virus-hunter has his own institute and a trailblazing strategy to conquer AIDS

December 1, 1999 Interview by Lark Lands, PhD

It is fitting that *POZ*'s 12-part Countdown Y2K series—setting a research agenda for the new millennium—concludes with an interview with Robert Gallo, MD. Gallo, HIV codiscoverer and director of the Institute of Human Virology at the University of Maryland in Baltimore, is one of the great forces of AIDS research. Looking back, it seems that the legendary controversies that have rocked his career often arose because he was too far ahead of his time and too outspoken for the stodgy world of medical science. Here, Gallo gives an inside look at his institute's most promising investigations, which include everything from immune-system messengers to therapeutic vaccines to a compound made from pregnant women's urine that may prove to be next year's big sleeper. (See "Gallo's High Five," below, for the short-list of his research projects.)

Lark Lands: What do you consider the most important goals in AIDS research today?

Robert Gallo: At the top of the list would be cheap, nontoxic, safe and easy therapies for infected people, as well as an effective vaccine to prevent new infections. And I think we're moving toward hope on both fronts.

However, to achieve these, we must continue to vigorously pursue studies of the basic biology of HIV—what the virus does, how it does it, and all the ways it causes harm and eventually leads to AIDS. We also need to better understand innate immunity, especially the natural defense mechanisms that occur within hours of exposure to any pathogen, possibly via chemokines [a type of immune-system messenger]. The best therapies will be based on biological control of the virus [a process triggered by tools—whether natural or synthetic—that allow the body to contain HIV].

In the industrialized world, we need these new biologically based approaches because of all the long-predicted problems we're now seeing with HAART. As with cancer, the longer you continue intensive drug combinations, the more problems you see with toxicity, compliance and the resistance that equals failure. In the developing world, we need simple, inexpensive approaches that will not require intensive medical monitoring. Even if the current drugs were made available where HIV is an overwhelming threat, they would not be the answer. The systems of medical care needed to deliver the drugs, educate people and then monitor for toxicity, resistance and compliance are not there. You can't just hand people drugs and then not follow up. So what we need are much simpler approaches.

Last but not least, we urgently need better ways of treating people in the inner cities in the industrialized world. Too many are receiving inadequate medical care and ending up with only partial treatment. The result will be a lot of resistance and failure.

One new biological approach you're pursuing is the possibility of therapies based on our knowledge of beta-chemokines, the cell-produced chemicals that normally occupy the CCR5 receptor needed by HIV to infect cells.

Yes, two approaches are of great interest here. First, maximizing the levels of HIV-suppressive factors such as the beta-chemokines, since high levels are associated with both a lower risk of becoming HIV-infected and a slower rate of disease progression. The problem is that the body uses these chemicals in only very small amounts for cell-signaling—for example, to summon white blood cells to sites of inflammation. Used in larger amounts, they can wreak havoc with cellular communication and immune responses. However, chemokines can be modified to retain their anti-HIV potency while eliminating their signaling through the CCR5 receptor, making them less likely to cause unwanted effects.

We're particularly interested in attaching chemokines to glycosaminoglycans [a type of sugar molecule]. We've shown that in the test tube this increases chemokines' antiviral effects and may also decrease the risk of side effects. We now need to follow up with animal research, but it's been delayed because of lack of money and other researchers with whom to collaborate. We hope to have both soon. Ultimately, these designer chemokines could become very important new therapies.

The second approach we need to investigate is how to downregulate [decrease the number of] chemokine receptors such as CCR5. Since HIV upregulates these receptors via the Tat protein that HIV's tat gene produces, we think that by vaccinating against Tat, we might downregulate them, and decrease HIV's chances for replicating.

Tell us more about your work on combining the Tat vaccine with an anti-interferon vaccine.

I think that therapeutic vaccines like those for Tat and alpha interferon are going to be of substantial benefit. Once it was shown that most of a person's T cells are not infected by HIV, even in late-stage disease, we knew that the virus must have other ways of suppressing the immune system. Now it's clear that two important factors are the Tat protein and alpha interferon, a cytokine [chemical messenger] that's produced in abnormally high amounts in HIV disease. Both of these compounds are toxic to the immune system. In the test tube we've seen that they reduce T cells' ability to proliferate and fight invading microbes, while they also trigger T cell apoptosis, the cellular suicide that's a major cause of T cell loss. People in late-stage disease or those who are progressing rapidly have high levels of these compounds, while long-term nonprogressors have high levels of antibodies to Tat.

So Daniel Zagury, of the University of Pierre and Marie Curie in Paris, and I thought that vaccines

that stimulate production of antibodies to Tat and alpha interferon might help to restore the immune system's ability to control the virus, even when it's hiding in tissues current drugs don't reach. The Tat toxoid developed by the French company Neovax under Zagury's direction is a modified form of Tat that boosts antibody production without stimulating viral replication or poisoning the immune system. We have four years of results from Zagury's trials using the Tat toxoid in Europe and Israel, and three years using inactivated alpha interferon, all of which are promising.

Now we need large U.S. trials that combine the two, which we think is how they'll work best—just as multiple antiretrovirals best suppress HIV. In preliminary research, we've shown that in untreated people given the vaccines, CD4 counts stabilize, although their viral loads aren't dramatically affected. This wouldn't be enough for people in late-stage disease, but it might slow disease progression by restoring the capacity of T cells to respond. This vaccine combo should be inexpensive and probably needs to be given only four times a year, making it realistic for the developing world.

You're also encouraged about the possibility of a new preventive vaccine approach.

Yes, we want a vaccine that can quickly move from concept to clinic. Our best hope is to stimulate immunity in several different ways at once. We think that our candidate vaccine will combine three things. First, David Hone and George Lewis of our institute have developed a new, inexpensive, oral vaccine-delivery system called Bacto-fection that can be used to stimulate mucosal immunity [in the cells of the body's linings]. They have genetically engineered weakened strains of intestinal bacteria such as Salmon-ella to carry viral genes into gastro-intestinal cells, which will then produce a protein normally found in HIV's coat. This will induce an immune response against HIV in the GI tract, where sexual infection takes place.

Second, Anthony DeVico, also of our institute, is working on attaching gp120, a protein found on HIV's surface, to the CD4 molecule [present on the surface of CD4 cells] to open up new sites on the HIV envelope where antibodies can attach. In monkeys, this promotes a large amount of neutralizing antibodies throughout the body, something that many researchers be-lieve would be required for an effective vaccine. We need further research since there is a theoretical risk that antibodies to CD4 could develop, but so far we haven't seen problems in monkeys.

And third, the Tat-toxoid vaccine could prevent the virus from using Tat to cripple the immune system's response to HIV. By doing all three together, we think that broad-based immunity could be created, and the combined approach should be sufficiently inexpensive to be used worldwide.

You've long pioneered research into agents that inhibit the body's cellular enzymes needed for HIV replication, rather than simply focusing on drugs that suppress the virus' reverse--transcriptase and protease enzymes. What looks promising?

Years ago, my team—most notably, Franco Lori—did work on hydroxy--urea, a chemo-therapy that targets a cellular enzyme that makes building blocks for DNA. The hope was that the virus will

need more of the building blocks than the cell will, so that decreasing the building blocks will hurt the virus more than the cell. Back then we showed that hydroxyurea has a synergy with ddI [Videx] since ddI works as a fake DNA building block—if you lower the number of normal building blocks with hydroxyurea, then more of the fake building blocks will be used by the virus. And the fake ones don't work for viral replication.

The same idea is now being pursued with other agents that may be less toxic than hydroxyurea. One that our institute is interested in is a natural compound called resveratrol [see "Days of Wine and Doses"]. Another uses a combination of mycophenolic acid, another drug that depletes building blocks, with abacavir [Ziagen] [see "Less Is More"]. Drugs in this class are exciting because—in contrast to compounds aimed directly at HIV, which induce viral mutation—the body's cells are unlikely to mutate to favor the virus' survival. These agents get us away from the same viral-enzyme inhibitors that always come with the same problems.

Word has it that you may soon make a major announcement about the compound in pregnant women's urine that you have been working on.

Yes, we've made important progress on this. We've now specifically identified it, verified the results that come from it and discovered how to synthesize it. In the first half of 2000, we'll be reporting on this in great detail. All I can say for now is that it's a natural product with effects that might be very beneficial in the late stages of both HIV disease and cancer, in part because of its ability to promote the growth of blood cells. And yes, as soon as I can say more, *POZ* will be among the first to know.

GALLO'S HIGH FIVE

1. Designer Chemokines
Synthetic versions of the normally cell-produced chemical messengers that help block HIV from infecting cells.

2. Combined Tat-toxoid and Anti-interferon Therapeutic Vaccine
Works against an HIV-produced protein and a body-produced chemical; may strengthen T cell response to HIV in already infested people.

3. Preventive Vaccine
A three-way approach that combines an HIV protein/receptor molecule duo, a Tat-toxoid vaccine, and a boost to immunity in the body's lining via a new oral delivery system.

4. Drugs Targeting the Body's Enzymes Needed by HIV
Resveratrol, a compound in red wine, and a combination of mycophenolic acid with the existing antiretroviral drug, abacavir.

5. A Treatment Derived from Pregnant Women's Urine

May work against HIV infection and cancer, partly based on its ability to promote blood-cell growth.
