Towards an HIV Cure

Researcher and clinician Steven G. Deeks, MD, explains the cure science and gives us reasons for hope.

November 13, 2012 By Oriol R. Gutierrez Jr.

Tell us about the IAS working group and the report. The objectives were to have a diverse international group of scientists outline the obstacles to a cure and to develop a road map of how we as scientists might address those obstacles. We hope that through this strategy we will engage the community, inspire people to work in this area and use this document to raise interest and perhaps funding.

The group identified several key priorities. We need to know where the virus resides in people who are on long-term therapy—what types of tissues, what types of cells. These are things we have surprisingly little information about. We also need to know where the molecular pathways are that get turned on within a cell that force a virus to go into hiding and stay there. This gets down to some of the details about how HIV DNA—and in fact how DNA in general—is regulated.

We need to figure out what role the immune system has as a mechanism for those systems. Does chronic inflammation contribute to why HIV persists indefinitely?

We need to understand why certain people who acquire HIV appear on the surface to have been cured of HIV, the so-called elite controllers. We need to understand the mechanisms that account for that.
We need to come up with ways to measure the virus. Very few cells contain true replication competent virus, and measuring these cells will become a big issue in terms of doing clinical trials.

And finally we need to identify agents that sort of interrupt the various mechanisms of persistence, and [then we need] to move them into the clinical trial setting.

At this point, the group has no specific future tasks, but the work that the group is hoping to inspire is only just getting started.

What is your role in the Martin Delaney Collaboratory?
Recognizing that the cure was going to be a major part of the future HIV research agenda, the [National Institutes of Health, the NIH,] a few years ago funded three collaboratories [under the umbrella name the Martin Delaney Collaboratory, named in honor of the late AIDS activist].

These are three large groups of researchers, each with a different focus. CARE, the Collaboratory of AIDS Researchers for Eradication, works on the molecular biology of HIV latency. Defeat HIV, the Delaney Cell and Genome Engineering Initiative, works on developing gene therapy approaches.

And then there’s DARE, the Delaney AIDS Research Enterprise, which I codirect with my colleagues. Our focus is on harnessing the immune system to prevent persistence or to clear the virus.

Please explain your disulfiram research.
The primary barrier to a cure is the fact that the genetic information for HIV gets integrated into long-lived CD4 cells, so they basically exist for years and years and become silent. To cure people, we need drugs that activate this resting HIV, forcing it out of its hiding place. This in theory should result in the death of the infected cell.

A few years ago, Bob Siliciano found that disulfiram—[better known as Antabuse, which is used to treat alcohol dependency]—reverses HIV latency in cell culture. Through mechanisms yet to be defined, the drug appears to activate HIV from resting cells. The level of drug exposure necessary to cause this effect is similar to that obtained when the drug is given to people with alcohol problems.

Since this drug has actually been around for almost 60 years and is clearly safe, at least in people who don’t drink, we designed a series of clinical trials to advance this idea into patients.

We first performed a pilot study to confirm its safety. We found in that study that the drug might increase HIV production. With funding from amfAR and now the NIH, we are about to launch a more definitive study to see if this drug actually might contribute to a cure.

Why are you studying elite controllers?
There are two types of cure: a functional cure in which the patient’s immune system controls the virus and a sterilizing cure in which all virus is removed from the body. We think the former is
possible because about one in 100 people who have HIV essentially appear to have a functional cure. These so-called elite controllers have undetectable viral loads in the absence of therapy and generally remain undetectable for years to decades without therapy.

Based on work done by our group and others, [we now know that] about 50 percent of these individuals are controlling because they have powerful HIV-specific T-cells. Based on this finding, there’s been some interest in trying to develop vaccines that generate such T-cells.

Our group has been interested in two completely different questions. First, what is the mechanism of control in the other 50 percent, those people who don’t have evidence of strong, HIV-specific T-cells? Knowledge gained in these studies might lead to novel interventions aimed at curing people.

Second, are elite controllers truly protected from getting any HIV-related disease? Along these lines we’ve found that many elite controllers indeed have chronic inflammation, perhaps early heart disease and maybe even some subtle immunological abnormalities. Based in large part on that last series of observations, our group is now looking at whether or not treating elite controllers with therapy might be beneficial.

The study of inflammation has been the driving force for our group since 1996. We became interested in inflammation as an explanation for why some people with drug-resistant HIV do well in therapy. This work led to our interest in studying inflammation in elite controllers, and more recently to determine if chronic inflammation contributes to early heart disease and/or HIV persistence during long-term therapy. Chronic inflammation is central to much of what happens in untreated and treated disease. We’re trying to figure out why that is and what to do about it.

What still drives you?
I truly enjoy my job. There is a picture of me at work with the comment, “Thank God it’s Monday.” I have the fortune every day of working with a wonderful group of talented and highly committed people. I also interact in the clinic and in the research clinic with a group of highly engaged patients. HIV care and HIV science are very dynamic. There are always interesting questions to address.

My job is basically the same as it’s been since I started this work in 1993. I was hired as a part-time clinician and to help out in various clinical research projects, most of which were “translational” in nature and involved the link between the laboratory and the clinic. The only thing that has changed since I arrived in 1993 is that my clinic time has been reduced slightly and our research program has grown. The questions often change, but they have remained very much grounded in our clinic and in our local community.

We are now working on what will likely be the most challenging question: Can HIV be cured? Timothy Brown (a.k.a. the “Berlin Patient”) has moved to San Francisco and joined our research cohort. His presence has inspired our team and collaborators to work on issues related to the cure. He is in many ways the public figure of what we have been doing for years, which is working closely with the HIV community in performing cutting-edge and, we hope, highly relevant
research.

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