DESTINATION: CURE

by JEANNIE WRAIGHT

Talking "Cure"

WHAT ARE THE BARRIERS TO CURE RESEARCH

Nobel prize Laureate and world renowned HIV researcher Francoise Barré-Sinoussi recently made the statement that she does not believe an HIV cure is possible. As a co-discover of HIV, this statement carriers a lot of weight. So, I sat down with Dr. Harold Smith, PhD, a professor at the University of Rochester and faculty member for twenty-nine years, to pose the question "Is an HIV cure possible?" in light of Barré-Sinnoussi's statement.

In part I of this two-part interview Dr. Smith, discusses his research on ABOBEC3G and his new HIV therapies/eradication strategies, and the problems he's faced in moving a potential cure for HIV forward. Early in his career, Dr. Smith became known as one of the leaders in the field of APOBEC; indeed, he was one of the youngest of this field at that time and he continues to make significant contributions.

In part II, to be featured in an upcoming issue, Dr. Smith explores the idea of whether or not a cure is possible and whether or not, by looking at cure the same way that we look at treatment, in terms of what is acceptable, we may be setting the bar too high and setting ourselves up for failure.

Jeannie Wraight: Can you tell us about ABOBEC3G, Vif, and your research on them?

Dr. Harold Smith: ABOBEC proteins have a curious quality to them. They are involved in many different functions in the cells. One that really caught my attention was ABOBEC3G.

Vif (viral infectivity factor), is an HIV protein. It's been studied for about twenty-five years and had various functions ascribed to it but nothing with great certainty.

It was discovered that the purpose of Vif was to find and destroy ABOBEC3G.

I realized this was a problem that my lab could contribute to. Thirty years ago I began switching my lab, over time, from cardiovascular disease to where it's now, one hundred-percent-focused on HIV. What was needed was to try to apply this science toward developing new drugs since Vif seemed to have such an important role in killing our host defense. The APOBEC host defenses, left alone, would completely devastate the coding sequence of HIV, mutating HIV and wiping it out.

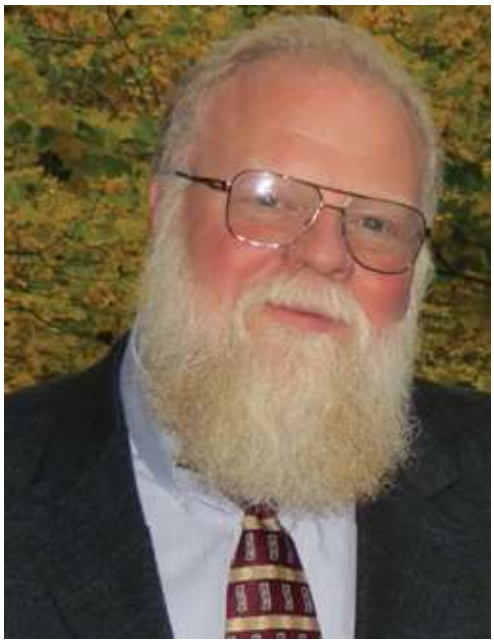
Without Vif we could defend ourselves against HIV, in which case it's a very important to validate this hypothesis.

I now do academic research in my lab at the University of Rochester which is very fundamental to how molecules and enzymes like ABOBEC3G work. I also have a company full of scientists at OyaGen dedicated to finding out what are the best drug-like chemistries to enable anti-viral activity through APOBEC3G and determine their safety. I formed OyaGen to develop new drugs that would bind to Vif and prevent it from destroying our defense mechanisms in order to stop HIV.

OyaGen is probably, conservatively speaking, three years away from entering phase I clinical trial with the first drugs that prevent Vif from destroying ABOBEC3G. This is a totally new drug target on HIV, a genetic hit that HIV cannot survive because our lead compound prevents it from coding for its own proteins. So if not a mechanism for eradicating HIV, then it certainly is going to be a very important mechanism for blunting any kind of infection and preventing the expression of infectious virus from viral reservoirs.

How have the dynamics surrounding the search for a cure affected your research moving forward?

We were recognized early on, about five, six years ago, by the pharmaceutical industry as having the most advanced Vif drug development program. OyaGen has been working on small molecule drug development since 2010, though the company started in 2003. We were constantly told by the Pharma industry that we should move further along: "There's an interesting experiment we would like to see you do. We know it's going to cost a lot of money, we know you don't have the money, but we'd like you to do it anyway and we welcome you to come back once you've accomplished it." And as we accomplished these requests each time; two men pick up the goalpost and walk ten yards further along and ask us to achieve another $100,000 and $300,000 experiment. The real issues are perceived as being "too early," which is a term used by Pharma and investing firms to say at the discovery and development phase their money is at too much risk. I have to conclude that they are very satisfied with what they have and are doing therapeutically and there's no urgency to evaluate new targets that may be curative. Pharma has a lot of money invested in current ART and good patent protection. Why spoil this with something that's curative? I've raised this issue and I've been told "No, no, no, everyone's very interested in cure." I would imagine being at the board meeting where the lab director comes in and says, "Here's the story—Vif dimerization antagonism is absolutely curative, no doubt about it. You give this to patients for a few months, there's no living virus, everything is replication incompetent, you're functionally cured." Now there's the reality that they may be free of ART. What would they do in contemplating the financial impact on what was a sure stream of revenue from ART and drugging familiar HIV targets? Cure is a disruptive technology for this industry.



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Some say that the current funding systems aren't set up for cure research and that it's slowing the progression of potential cure agents and strategies. Has that been your experience?

As I said I'm new to the HIV field. When I first started writing grants for my HIV research involving ABOBEC3G and Vif, I was coached by experts in the field to be careful how to phrase goals in research, new mechanisms, or developing a new drug target. They told me to not have a goal of eradicating the virus and not to use the words "kill" or "stop" the virus, [but] rather have more modest goals of inhibiting replication or reducing the spread of infection. Definitely [I was told that] a hypothesis for what might be curative should not be proposed because that would come across as ungrounded in the reality that cure had not been achieved despite decades of "research."

It was extremely taboo.

In a grant, I lead with a hypothesis. For example, my hypothesis is [that] when I treat HIV with a drug that prevents Vif from destroying APOBEC3G, 3G will cause devastating mutations to HIV and in a few cycles of replication the virus will be dead. The argument is that this has the potential of being curative. From there I write my specific aims that outline the research approach and milestones. Previously, if you could not hypothesize curative approaches, you proposed therapy in the grant and hoped for more. The culture of peer review and grant writing encouraged scientists to limit their expectations. The sentiment expressed in the media is that now is the time for cure, as perceptions have changed and, where we once did not *dare* imagine [a] cure, now we are seeking new approaches. If this is true, then although decades of science have led to success in extending the lives of people who have HIV, this period also reflects massive effort that failed to find a cure. I would argue that the statement is not entirely accurate. While responsible researchers limit their hypotheses in grant proposals to what can be tested, as no one knows what will be curative, even though "cure" was the word that could not be said, there remained every possibility that something or combinations of approaches could prove to be curative.

So the grant structure was not geared towards cure research?

Not at all. Then all of a sudden, there were several claims and talk of "cures." Even though NIH didn't produce a clear understanding of the definition of cure or what constituted cure research, $100 million was appropriated by President Obama for cure initiatives. The system wasn't set up to address cure in hypothesis-driven and mechanistic-type research. A new Research Funding Announcement (RFA) was released for cure research and when I asked the program officer in charge about our efforts in evaluating Vif, his response was, "No, that is not the kind of target we are considering for cure." How did NIH know what drug targets were appropriate for cure?

Do you see this changing?

Much will have to change in the peer review system at NIH in order for innovation to have a chance to prove or disprove itself.

Jeannie Wraight is the former editor-in-chief and co-founder of HIV and HCV Haven (www.hivhaven.com) and a blogger and writer for TheBody.com. She is a member of the Board of Directors of Health People, a community-based organization in the South Bronx and an advisor to TRW (Teach me to Read and Write), a community-based organization in Kampala, Uganda. She lives with her husband in New York City.