TREATMENT HORIZONS

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The Deeper End of the Ocean

HOST RESTRICTIVE FACTORS CREATE RESEARCH EXCITEMENT

The doors on viral host restrictive factors (HRFs), the means by which our cells are designed to resist infection, are being pried open by scientists who see the next round of therapeutic advances for treating HIV just within reach.

Currently, all HIV therapies function by interrupting the HIV replication process while leaving latent viral reservoirs intact. According to researchers, eliminating these HIV reservoirs will be essential to any eradication strategy. Host restriction factors are being studied as potential eradication strategies for HIV, ones that would address HIV replication (including resistant virus) and latent HIV.

Host restrictive factors (HRF) are cellular proteins. They act as natural defense mechanisms for individual cells against viral infection, preventing a virus from successfully infecting a cell. There are different forms of these proteins and each block HIV at different stages of the viral life cycle.

A3G

Arguably the most promising of the host restrictive factors are those in the APOBEC3 family, whose job it is to identify and mutate foreign genetic material (HIV RNA) in the cell. HIV is well aware of these APOBEC host restrictive factors and expresses its own defense in the form of a viral protein known as Vif. Vif's sole purpose is to disable APOBEC proteins, deflecting their action to allow HIV to infect the cell and replicate.

Research on APOBEC3G (A3G) modulation, which is currently in the preclinical stage, has been facilitated by support from the National Institutes of Health, The Bill and Melinda Gates Foundation, the Empire State Development Fund, the New York State Retirement Fund and at OyaGen, a drug discovery biotechnology company spinout from the University of Rochester.

OyaGen is developing several compounds that prevent Vif from disabling A3G and thereby allowing A3G to prevent HIV infection of cells. These classes of drugs include A3G agonists, Vif destabilizers and Vif dimerization antagonists. The YouTube video on some of the research presented at ICAR and the AIDS Free World meeting that took place in San Francisco from November 3–5, 2013, can be viewed here: http://www.youtube.com/watch?v=P1ODXikMmHk.

"In 2005 while working with Dr. Xia Jin at the University of Rochester, our studies suggested to us that long-term nonprogressors expressed more A3G than our uninfected control patients" said Dr. Smith. "Then contract work between OyaGen and Dr. Hui Zhang at Thomas Jefferson University showed that preventing HIV Vif from dimerizing protected A3G from Vif-dependent degradation and blocked viral replication. We know HIV cannot survive without Vif and now OyaGen has the lead compounds to deprive HIV of Vif, thereby enabling our natural APOBEC host defense to prevent the spread of infection."

If further research into A3G agonists carries on its current course, they may be a viable option for treatment in the near future. Leading scientists in this arena believe that, unlike the available HIV medications, resistance to Vif dimerization antagonists and A3G activators is unlikely. This would allow for a potential new treatment for heavily treatment-experienced HIV patients who currently have limited to no treatment options due to drug resistance to the available ARVs. These drugs may also be possible eradication strategies that can affect the hidden reservoirs that are driving inflammation. Inflammation contributes to the exacerbation of cardiovascular disease and metabolic consequences.

A recent study published this year by Iraj Hosseini and Feilim Mac Gabhann from Johns Hopkins University reported that overexpression of A3G or interfering with A3G-Vif binding can effectively block HIV replication. The authors developed a mathematical model that suggested that stem cell therapy resulting in a high proportion of A3G-overexpressing CD4+ T cells can effectively inhibit HIV replication in vivo.

A study published this year by Richard D'Aquila from the Vanderbilt University School of Medicine extends the early work of Smith and Jin by showing that elite controller's resting memory T cells had very high levels of A3G protein and the very low levels of provirus. Vif-positive viruses with more A3G have decreased HIV's ability to infect cells. This supports the hypothesis that HIV control is strongly associated with increased levels of cellular A3G.

Illustration by Timothy J. Haines

HDAC Inhibitors

While the momentum for A3G is definitively growing, a great deal more attention is being paid to another antiviral strategy, HDAC (histone deacetylase) inhibitors, currently used to fight cancer, epilepsy, psychiatric issues, and other illnesses.

HDACs are a large family of enzymes that the cell uses to close down genes in our chromosomes to prevent their expression. Inhibited HDACs results in reactivation of gene expression. As HIV integrated into chromosomes of the cells in reservoirs is hidden, the virus needs to be made visible. HDAC inhibitors enable HIV to be expressed.

HDAC inhibitors are being studied to test the hypothesis that they can be used to "flush" HIV out of resting cells. It is important to keep in mind that while HDAC inhibitors can cause expression of viral components and release of virus from otherwise quiescent reservoirs, the integrated HIV genome will remain and can only be eradicated if the reservoir cells are killed. These viral reservoirs are a main barrier to eradicating HIV but releasing active virus from the reservoirs as a means of revealing their presence to the immune system comes with the price of viremia.

Several studies testing HDAC inhibitors have shown promise and have received a good deal of attention. One eight-patient study showed that Vorinostat, an HDAC inhibitor used to treat cancer, activated HIV in latent cells. However, the study did not show the size of the HIV reservoir decrease or the infected cells

being killed. Another twenty-patient study achieved the same results.

Several potential problems exist with HDAC inhibitors. When used for cancer treatment, serious adverse events are experienced by some patients taking vorinostat. It is unknown at this time the level of toxicity that may occur in HIV patients and what effects may ensue. For example, HDAC is responsible for keeping the integrated HIV in a resting state, but it is unknown for what other viruses HDACs perform this same function. Using vorinostat or other HDAC inhibitors to awaken HIV may cause other retroviruses that have been passed down in humans to reactivate and combine with HIV. Thus fa,r this has not been seen in the people who have participated in the clinical trials of vorinostat, but the long-term effects remain unknown.

"HIV cure strategies and the ensuing clinical protocols will likely involve many agents, just as suppression strategies evolved to involve agents targeting multiple steps in the viral life cycle. While the transcriptional activators, HDAC inhibitors, play a key role in activating HIV from the latent pool, a variety of host-defense factors can potentially ensure that this endogenous infective virus is unable to progress to a point of a new productive infection," said Dr. Richard Ogden, Executive VP of Strategic Development at OyaGen.

A Call for Innovative Thinking

What is difficult for many to understand is the pharmaceutical industry's inflexible focus on developing modifications of traditional therapeutic drugs that past drugs clearly indicated do not bring about a cure. Innovative thinking and a broad exploration of new ideas with rapid triage is the rational course of action to achieve eradication in the immediate future.

The potential shown by A3G agonists and Vif dimerization antagonists to date is promising. Further studies in humans are needed to move research forward on these drugs. Although funding directed at HIV eradication research is scarce, some sources do exist to further promising research on A3G including the Martin Delaney Collaboratory. The NIH has recently redirected $100 million dollars of research money to be used for HIV cure research. Research on viral host restrictive factors must be included in budgets directed towards cure research.

While public campaign initiatives like "Getting to Zero" and an "AIDS Free Generation" continue to provoke speculation that the end of the epidemic is near, the question for biotech companies like OyaGen working on razor-thin budgets is whether or not Congress will afford the NIH the resources necessary for more cure research including research targeted on drug discovery for Vif and A3G and other viral host restriction factors.

Scientific investigations that challenge HIV's insidious ability to evade the current paradigm of antiretroviral therapy are needed as the epidemic is definitively advancing in populations that are suffering from disproportionate vulnerabilities. Michel Kazatchkine, U.N. Special Envoy for HIV/AIDS in Eastern Europe, said, in an interview reported in Reuters, "We are a bit in disarray. We don't know quite what it is that we should do. Here we are, we have all the technology, we have extraordinary scientific progress, and we just cannot translate that into making a difference in these populations."

Mariel Selbovitz, MPH, serves as the Chair of the Cornell ACTG Community Advisory Board and has authored over thirty abstracts and articles.

A former member of ACT UP NY, David Miller is an AIDS treatment activist and current member of the Cornell ACTG CAB. He is on the Community Access Board of OyaGen, one of the subjects of this article.