Toward a Cure: The Potential of Therapeutic Vaccines

April 10, 2012 By Tim Horn

While gene therapies that render the immune system impervious to HIV and drugs that potentially purge the virus from resting CD4 cells continue to be watched closely by AIDS cure researchers and advocates, therapeutic vaccines may serve an important supporting role in these efforts, according to a commentary published by activist Richard Jefferys in the Spring 2012 TAGline newsletter.

“After a period in which enthusiasm regarding the prospects for therapeutic vaccines waned,” Jefferys writes, “the recent resurgence in interest in research aiming to cure HIV infection has offered new reasons to pursue their development.”

Notable therapeutic vaccines for the virus use HIV particles, sometimes paired with other viruses, or largely intact HIV, to jumpstart the immune system’s perceived ability to control viral replication in the body. Such vaccines have been conceptualized and explored since the mid-1980s. “But the first efforts toward this goal quickly mired therapeutic vaccine research in controversy,” Jefferys writes, “casting an initial pall across the field that was compounded by the failure of any candidate to show significant efficacy.”

Jefferys explains that therapeutic vaccines are now in their third—and potentially most critical—era of development, noting that the first two eras didn’t pan out for important reasons.

In the first era, dating back to the 1980s and early 1990s, therapeutic vaccine candidates of the day faced significant hurdles that were unknown at the time. For example, it was once assumed that HIV is mostly dormant during the asymptomatic and untreated years of infection and that CD4 cells lacked the ability to respond to HIV. Subesequent findings proving these hypotheses wrong, Jefferys writes, "seriously called into question the idea that adding more HIV antigens into the mix via therapeutic vaccination—when the virus itself was failing to induce protective immunity—would be beneficial."

In the second era, with viral load technology and combination antiretroviral therapy (ART) widely available, therapeutic vaccination plans evolved. One approach was to bolster the immune response to HIV while study volunteers were keeping their viral loads undetectable using available ARVs, followed by treatment interruptions to test the immune system’s ability to control HIV replication in the absence of therapy.

“Once again,” Jefferys explains, “scientific advances served to undermine the rationale behind these studies. Specifically, the idea that [ART] could be safely interrupted as long as CD4 T-cell counts were maintained was shown to be erroneous by the sobering results of the Strategic Management of Antiretroviral Therapy (SMART) trial. SMART had the specific goal of assessing whether intermittent, CD4-guided ART could be as effective as continuous ART, but the trial had to be stopped early because individuals in the intermittent arm experienced a doubling in risk of illness and death. Analyses demonstrated that these events were associated with inflammation resulting from unsuppressed viral load, prompting additional investigations into the link between inflammatory markers, uncontrolled HIV replication and health outcomes.”

In the current third era, as Jefferys makes clear, the various shortcomings of therapeutic vaccine research completed thus far mean that the bar has been raised. “The key question has become, Is it possible for a therapeutic vaccine to generate HIV-specific immune responses capable of completely containing viral replication when ART is interrupted? This may seem like a dauntingly high hurdle given results to date, but it dovetails with emerging research that has recently resurrected therapeutic HIV vaccines for the third time. This research is in pursuit of the ultimate goal: a cure for HIV infection.”

One potential avenue of research: using therapeutic vaccines to bolster the CD8-cell response that may be necessary to kill CD4 cells that have had their dormant HIV awakened using HDAC inhibitors or other reservoir-purging drugs. One paper reviewed by Jefferys, presented at the recent 19th Conference on Retroviruses and Opportunistic Infections in Seattle, “presented compelling evidence that simply rousing HIV is not sufficient; CD8 T-cells are needed to deliver the *coup de grace* and kill the infected cells.”

Jefferys concludes: “Despite the history of controversy and uncertainty, the ascendancy of cure research has provided a strong and scientifically sound rationale for further studies of therapeutic HIV vaccines. The goals are now far clearer: to achieve containment of HIV replication and prevention of disease in the absence of ongoing treatment (now described as a ‘functional cure’), or complete elimination of the virus (a ‘sterilizing cure’).”

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