

# TAG HIV Basic Science, Vaccines, and Cure Project Blog

By Richard Jefferys, Project Director at Treatment Action Group (TAG). Established thanks to a grant from the Michael J. Palm Foundation.

## Recruiting Natural Killer Cells to Target HIV Persistence

An important goal in HIV cure research is the identification of immune responses that might be induced or enhanced to promote clearance of virus-infected cells. The main focus of this work has been on adaptive immunity—components of the immune system that can specifically recognize HIV, which include CD4 T cells, CD8 T cells, B cells and antibodies. But there is growing interest in cells considered part of the innate immune system, particularly natural killer (NK) cells. NK cells have the potential to destroy virus-infected cells by several mechanisms, including the identification of generic signs of cellular distress or infection, or via antibody-mediated recruitment to a target cell (known as antibody-dependent cellular cytotoxicity/ADCC).

Over the past few months a number of studies have been published that support the idea that NK cells can play an important role in controlling virus replication. In the journal *Nature Medicine*, Nicolas Huot and colleagues describe evidence that NK cells contribute to suppression of SIV replication in the lymph nodes of African Green Monkeys (AGMs), a host species that does not experience pathogenic consequences from the infection.

In experiments comparing nonpathogenic SIV infection of AGMs to pathogenic infection in macaques, NK cells were found to localize within and around lymph node B cell follicles—the major site of virus replication and persistence—in AGMs, but were scattered randomly in macaques, with no accumulation in follicles. NK cell numbers in lymph nodes also progressively declined in macaques, while being maintained at pre-infection levels in AGMs.

Additional analyses found that these differences were associated with an increased frequency of NK cells expressing CXCR5 (a receptor governing homing into follicles) and localized production of the cytokine IL-15 in the follicles of AGMs. The role of IL-15 was further confirmed by administration of an anti-IL-15 antibody, which depleted NK cells from the lymph nodes of the AGMs and led to a significant increase in SIV replication.

The authors write in their conclusion: “On the basis of our results, we anticipate that better comprehension of NK cell biology in lymphoid tissues, as provided here, will endorse the search for new NK cell–based immunotherapies for HIV infection.”

A review published in the journal *AIDS* in November covers some of the potential NK cell–based immunotherapies that are under investigation. A panoply of clinical trials are testing broadly neutralizing antibodies (bNAbs), which may have the ability to promote NK cell-mediated ADCC. In some cases bNAbs are being evaluated in tandem with latency-reversing agents, with the aim of depleting the HIV reservoir.

Also cited is the toll-like receptor 9 (TLR9) agonist MGN1703, which researchers at the University of Aarhus have shown can promote NK cell activation in HIV-positive people on ART. The same research group has also reported that NK cell responses may have been linked to an HIV DNA decline in some participants in a trial of the latency-reversing agent panobinostat.

Other NK cell–based immunotherapies in clinical trials include ALT-803, a modified version of the cytokine IL-15. The research group of Timothy Schacker at the University of Minnesota is conducting a small study involving ALT-803 administration to HIV-positive individuals on ART. A paper published in the *Journal of Virology* late last year describes a transient anti-SIV effect of the compound in macaques that were not receiving ART. Schacker and colleagues have also recently launched a trial in which individuals will receive infusions of NK cells from matched donors in combination with the cytokine IL-2.

The effects of the cytokine alpha interferon on HIV persistence are a major topic of interest at the newly-funded BEAT-HIV Collaboratory led by Luis Montaner at the Wistar Institute in Philadelphia. Last month in *Clinical Infectious Diseases*, Stéphane Hua and colleagues presented evidence that NK cell activation associates with a decline in HIV DNA levels in HIV-positive individuals receiving alpha interferon for the treatment of hepatitis C.

In sum, after a long period in the shadow of the better-known components of the adaptive immune system, NK cells are now emerging as potentially important players in HIV cure research. Results from the ongoing trials should soon shed additional light on how they might be able to contribute.

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