New combination immunotherapy plus ART expand innate cells critical to controlling HIV

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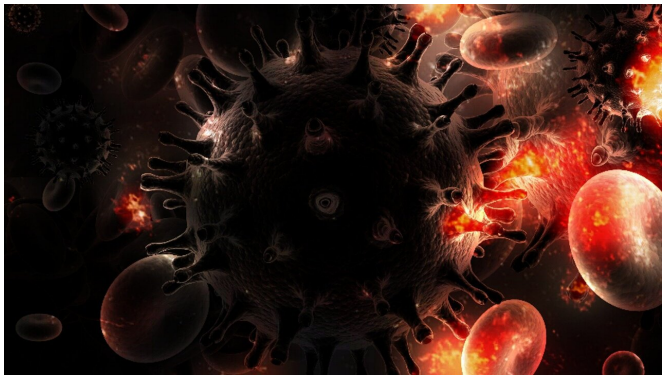

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Yerkes National Primate Research Center researchers in collaboration with Institut Pasteur have determined a combination immunotherapy of Interleukin-21 (IL-21) and interferon alpha (IFN?) when added to antiviral therapy (ART) is effective in generating highly functional natural killer (NK) cells that can help control and reduce simian immunodeficiency virus (SIV) in animal models. This finding, published online today in *Nature Communications*, is key for developing additional treatment options to control HIV/AIDS, which impacts 38 million people worldwide.

ART is the current leading treatment for HIV/AIDS. It is capable of reducing the virus to undetectable levels, but is not a cure and is hampered by issues such as cost, adherence to medication treatment plan and social stigma.

To reduce reliance on ART, the Yerkes, Emory and Institut Pasteur research team worked with 16 SIV-positive, ART-treated rhesus macaques. In most nonhuman primates (NHPs), including rhesus macaques, untreated SIV infection progresses to AIDS-like disease and generates NK cells with impaired functionality. This is in contrast to natural primate hosts of SIV, which do not progress to AIDS-like disease (Huot et al., *Nature Communications*, 2021). Determining why natural hosts do not progress or how to stop the progression is a critical step in halting HIV in humans.

The researchers compared ART-only treated animals with animals that received ART, IL-21 and IFN? to evaluate how the ART plus combination immunotherapy affected the amount of virus in the animals' tissue.

"Our results indicate the ART plus combo-treated rhesus monkeys showed enhanced antiviral NK cell responses," says first author Justin Harper, Ph.D. "These robust NK cell responses helped clear cells in the lymph nodes (LN), which are known for harboring the virus and enabling its replication and, therefore, the virus' persistence. Targeting areas where the virus seeks refuge and knowing how to limit replication facilitate controlling HIV," Harper continues. Harper is a senior research specialist and lab manager of the Paiardini research lab.

HIV treatment has historically focused on the role of T cells in immunity. "This proof-of-concept study in rhesus monkeys, which progress to AIDS-like disease in the absence of ART, demonstrates how certain NK cell activity can contribute to controlling the virus," says Mirko Paiardini, Ph.D. "This opens the door to designing additional treatment strategies to induce SIV and HIV remission in the absence of ART, and, ultimately, reducing the burden HIV is to individuals, families and the world," he adds. Paiardini is an associate professor of Pathology and Laboratory Medicine at Emory University and a researcher at Yerkes.

More information: Justin Harper et al, IL-21 and IFN? therapy rescues terminally differentiated NK cells and limits SIV reservoir in ART-treated macaques, *Nature Communications* (2021). DOI: 10.1038/s41467-021-23189-7

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