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Universal Tre-recombinase (uTre) specifically targets the majority of primary HIV-1 isolates

Hauber I.[1], Karpinski J.[2], Schäfer C.[1,3], Chemnitz J.[1], Hofmann-Sieber H.[1], van Lunzen J.[3,4], Buchholz F.[2], Hauber J.[1,3]
[1]Heinrich Pette Institute, Antiviral Strategies, Hamburg, Germany, [2]TU Dresden, Medical Systems Biology, Dresden, Germany, [3]German Center for Infection Research (DZIF), Hamburg, Germany, [4]University Medical Center Hamburg-Eppendorf, Section Infectious Diseases, Hamburg, Germany

Background: HIV-1 integrates into the host chromosome and persists as a provirus flanked by long terminal repeats (LTR). To date, treatment regimens primarily target virus attachment, virus-cell fusion or the virus enzymes, but not the integrated provirus. Thus, current antiretroviral therapy (cART) cannot eradicate HIV-1, a fact that highlights the urgency of pursuing new strategies to find a cure for HIV/AIDS. Previously, we engineered an experimental HIV-1 LTR-specific recombinase (Tre-recombinase) that can efficiently excise integrated proviral DNA from infected human cell cultures. Subsequently, we demonstrated highly significant antiviral activity of this HIV-1 subtype A-specific Tre in humanized mice. Broad clinical application, however, requires availability of a Tre-recombinase that recognizes a majority of clinical HIV-1 isolates.

Methods: We employed substrate-linked protein evolution to engineer universal Tre-recombinase (uTre), recognizing the LTRs in a majority of clinical HIV-1 isolates (>94% of HIV-1 subtype A, B, and C). The activity of uTre was subsequently analyzed in cell lines and primary cell cultures, as well as in HIV-infected humanized mice.

Results: Here we demonstrate the absence of cytopathic and off-target effects, as well as pronounced antiviral uTre activity. In particular, uTre expression resulted in decline of viral loads below the detection limit (< 20 HIV-1 RNA copies/ml) in "personalized" mice, which were engrafted with CD4+ T cells from HIV-infected patients.

Conclusions: The presented data suggest that uTre technology may become a valuable component of future eradication strategies to reverse infection and thereby provide a cure for HIV/AIDS.