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Latency reversal Agent (LRA) romidepsin reactivates latent virus in two rhesus macaque (RM) models of controlled SIV infection in the absence of antiretroviral therapy (ART)

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Background: Viral reservoirs represent a major obstacle for HIV cure research. A reservoir reactivation strategy is the “flush and kill”, in which LRAs reactivate latent virus and CTLs eliminate it. LRAs have limited efficacy, while immunosuppression impairs CTL ability to eliminate reactivated virus. Our goals were to assess in vivo romidepsin ability to reactivate SIV in two different models of controller RMs with functional immune responses and its effect on CTLs and viral control.

Methods: Three SIV_{smmFTq}-infected RMs received ART (PMPA; FTC; L-870812) for 9 months. After treatment discontinuation, the RMs controlled virus rebound and received 3 rounds of romidepsin, followed by CD8⁺ cell depletion. Two SIV_{sub}-infected RM spontaneous controllers received two rounds of romidepsin. Plasma viral loads were monitored with single copy assays. PBMC histone acetylation, IFN- γ production by CTLs and changes in T cells counts and their immune activation/proliferation status were assessed by flow cytometry. Romidepsin toxicity was monitored clinically and biologically; T-cell apoptosis post-RMD was assessed flow-cytometrically and by LDH ELISA.

Results: Romidepsin administration resulted in significant virus rebounds (up to 10⁴ copies/ml for SIV_{smmFTq} and 10³ copies/ml for SIV_{sub}) followed by gradual viral decline. Romidepsin was well-tolerated and induced a massive surge in T-cell activation and transient lymphopenia during the first week post-treatment. Lymphopenia resulted from cell redistribution and downregulation of surface markers rather than T-cell destruction. CD8⁺ cell depletion resulted in robust viral rebound (up to 10⁷ copies/ml) that was controlled upon CD8⁺ T-cell recovery. Romidepsin did not significantly affect CTL antiviral functions in vivo. Using mathematical modeling, we showed that a small fraction of latently infected cells were at the origin of virus rebound.

Conclusions: Using two different in vivo models of SIV control, we demonstrated romidepsin can reactivate the reservoir virus. The levels of virus replication, timing of virus rebound and rapid control of virus replication after romidepsin administration suggest the reactivated virus is replication-competent and romidepsin does not persistently alter CTL function. CD8⁺ cell depletion resulted in higher viral rebound compared to romidepsin administration, suggesting that romidepsin does not completely ablate CTL function. Altogether, our results show romidepsin can effectively reverse SIV latency.