1297 LATENT HUMAN HERPESVIRUS 6 IS REACTIVATED IN CHIMERIC ANTIGEN RECEPTOR T CELLS

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Background Cell therapies have mediated durable clinical responses for patients with cancer, but the risks associated with engineering therapeutic human cells *ex vivo* are still being understood. We currently lack a comprehensive mechanistic understanding of underlying toxicities observed in patients receiving FDA-approved T cell therapies, including recent reports of encephalitis caused by human herpesvirus 6 (HHV-6) reactivation.

Methods We combine comprehensive public data mining spanning petabases of genomic sequencing data (public RNA-seq, DNA-seq) to identify sources of viral reactivation from existing genomics sequencing studies. We complement extensive public data reanalysis with our own single-cell genomics experiments that simultaneously identify viral gene expression/reactivation with host gene expression programs.

Results Via petabase-scale viral genomics mining, we examine the landscape of human latent viral reactivation and demonstrate that HHV-6B can become reactivated in human CD4+ T cell *in vitro* cultures. Using single-cell sequencing, we identify a rare population of HHV-6 'super-expressors' (~1 in 300–10,000 cells) that possess high viral transcriptional activity in research-grade allogeneic chimeric antigen receptor (CAR) T cells. By analyzing single-cell sequencing data from patients receiving cell therapy products that are FDA-approved or in clinical studies, we identify the presence of CAR+, HHV-6 super-expressor T cells in patients *in vivo*.

Conclusions Our study demonstrates the utility of comprehensive genomics analyses to implicate cell therapy products as a potential source contributing to lytic HHV-6 reported in clinical trials. Further, our characterization of *in vitro* viral reactivation may influence the design, production, and monitoring of autologous and allogeneic cell therapies, and future prospective studies that account for HHV-6 reactivation in clinical products will determine whether these findings warrant changes to current manufacturing and clinical guidelines.

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