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Impact of HIV and Methamphetamine Use on the Nucleome in Individuals on Antiretroviral Therapy

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A major challenge in ending the HIV pandemic is the persistence of the latent HIV reservoir in antiretroviral drug treated (ART) persons. A compounding risk factor in HIV pathology is substance use disorder (SUD) which is known to decrease the efficacy of ART, and to accelerate progression to AIDS. We hypothesize that persistence of HIV reservoirs is encoded in the proviral location within the 3D architecture of the host genome (nucleome) and influenced by SUD-induced changes in epigenetic structures.

We have begun study of HIV integration site patterns, epigenomes and 3D-nucleomes in CD4+ T-lymphocytes derived from cohorts that differ in their exposure to methamphetamine and HIV infection status. CRISPR/Cas9-mediated gene-editing techniques are being used to dissect the impact of proviral integration sites.

Our studies to date of HIV proviral integration sites revealed distinct distribution biases with respect to orientation and position within genes in addition to placement of HIV integration sites relative to super-enhancers. Preliminary gene-editing experiments in primary CD4+ T-cells show that HIV LTR elements can drive hybrid transcript formation which can lead to increased cell survival.

Advanced 3D-nucleome mapping strategies will further define the interdependence of nuclear structure, proviral genomic location, regulatory elements, and single cell transcriptomes in short-term ex vivo cultivated patient-derived cells from both cohorts. These studies will also be extended to assess effects within methamphetamine users.