Contribution ID: **345** Type: **Oral Presentation**

Mathematical modelling of potential mechanism for the restoration of the T-cell homeostasis along with a sustained decay in viral reservoir upon infusion of CCR5 gene edited T cells in HIV infected subjects

Tuesday, 10 July 2018 11:00 (30 minutes)

Although antiretroviral therapy (ART) suppresses viral replication, patients still suffer from both low CD4 T-cell counts and HIV persistence, requiring them to remain on complex ART regimens for life. A naturally occurring 32-base pair deletion in the CCR5 gene, the major co-receptor for HIV entry, is associated with infection resistance.

In the study initiated by Sangamo Therapeutics, HIV-infected subjects received a single infusion of autologous CCR5-modified CD4 T-cells. Following infusion, we observed a sustained increase in the CD4 T-cells count (mean ~162 cells/μL) with a significant decrease in the HIV reservoir (median ~1 log 3yrs post infusion). Long-term persistence of CCR5-modified cells suggested their presence within long-lived CD4 populations, such as T memory stem cells (TSCM). To investigate the impact of persistence of "HIV-resistant" TSCM on immune homeostasis and the decay of the HIV reservoir, we developed a mathematical model of T-cell dynamics. The model follows a linear transition from the naïve to effector memory (TEM) state and includes thymic input of naïve cells, proliferation, death and differentiation rates for naïve and memory cells. Model fits to patient data pre- and post-injection and sensitivity analysis results that increased thymic output, an increased TSCM proliferation rate, a decreased central memory cell death rate, and an increased central memory transition rate played an important role in increasing the T-cell count and decreasing the HIV reservoir.

Finally, using a bi-phasic decay model, we show that purging and replacement dynamics of the CD4 T-cells population post infusion account for a significant fraction of the observed decrease in the HIV reservoir. Our results indicate that homeostatic processes can control HIV persistence, and that T-cell restoration post infusion of CCR5-deleted cells leads to the decay of the HIV reservoir.

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Session Classification: Modelling memory in physiological regulation

Track Classification: Minisymposium: Modelling memory in physiological regulation