

# VIDD Scientific Seminar Series

## Genetic Engineering of Human Hematopoietic Cells for Novel Clinical Applications



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Current efforts in our laboratory are focused on using gene editing to endow human hematopoietic cells with new, clinically relevant, functional activities. This work utilizes co-delivery of a designer nuclease and AAV donor DNA template to mediate homology-derived repair (HDR). In one effort, we aim to develop an autologous regulatory T cell therapy for severe autoimmune disorders. We introduced a constitutively active promoter into the *FOXP3* locus via HDR. This permitted us to bypass endogenous promoter silencing and enforce expression in CD4 effector T cells (Teff). High level, stable *FOXP3* expression converted Teff to Treg-like cells with immunosuppressive activity *in vitro* and *in vivo*. We next established a clinical cell manufacturing protocol enabling the transition to CMC process development. Efficient HDR was achieved across multiple donors, and edited cells were enriched to >95% purity and expanded 50-fold. Our pre-clinical, proof-of-concept and safety data support use of edTreg in a clinical trial for IPEX, and potentially, other autoimmune diseases. In parallel with work in T cells, we utilized gene editing to develop a B cell-based method to deliver protein drugs. We coupled CRISPR/Cas9- nucleases with AAV donor delivery to candidate safe-harbor loci in B cells to generate a durable population of drug or antibody-secreting cells (ASC) that produced high levels of exogenous proteins *in vitro* and *in vivo*. Our expanding data suggest that engineered human B cells engraft long-term and function *in vivo*, supporting future use of this platform for long-term delivery of protein drugs.

**Tuesday, February 5, 2019**

**3:00 - 4:00 pm**

**Pelton Auditorium**

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