A NON-HUMAN PRIMATE MODEL OF CYTOKINE RELEASE SYNDROME (CRS): TOWARDS IMPROVED SAFETY OF CHIMERIC ANTIGEN RECEPTOR (CAR) T CELL THERAPY

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Adoptive T-cell therapy using Chimeric Antigen Receptor (CAR) T cells has produced encouraging results in clinical trials. In particular, CAR T cell therapy against CD19, a molecule commonly expressed in B cell malignancies, produced complete remissions in 90% of patients with refractory B-cell acute lymphocytic leukemia (ALL). However, this novel and powerful immunotherapy is not without significant side effects, including cytokine release syndrome (CRS), which occurs in the majority of patients. CRS manifests clinically when high levels of inflammatory cytokines are released and includes fever, hemodynamic instability as well as neurologic toxicity. Although CRS is usually a self-limited complication, severe CRS can develop in >25% of patients and can be life-threatening. Given the fact that CRS is associated with increased levels of inflammatory cytokines, the treatment of CRS requires immunosuppressive agents, which are antagonistic to and thus diminish the effectiveness of CAR T cells.

We aim to create a non-human primate model using *Macaca mulatta* that closely recapitulates CRS observed in patients using CD20 CAR. Once the CRS model is established, our goal is to modify CAR T cells by imparting immunosuppression resistance, thereby allowing the use of immunosuppressive agents in patients to mitigate the severity of CRS without compromising the anti-leukemia potential of the CAR T cells.

We investigated the rhesus B-lymphoblastoid cell lines (B-LCLs) for CD20 expression and found it to be similar to human LCLs. We further demonstrated *in vitro* activity of human and rhesus CD20 CAR T cells against rhesus B-LCLs in chromium release and cytokine release assays. We subsequently transduced rhesus T cells to a high efficiency (60-75%) to express either green fluorescence protein (GFP) or the CD20 CAR and have expanded them *ex vivo* to quantities sufficient for autologous infusion and have currently begun to test their effects *in vivo.*