Lipid Nanocarrier-Mediated siRNA Targeting of Viral Genes in Burkitt's Lymphoma

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Burkitt's Lymphoma is an aggressive B-cell malignancy associated with Epstein-Barr virus (EBV) infection. Over 95% of the world's population is persistently infected by EBV. While current treatments for EBV+ BL rely on intensive chemotherapy, they often result in severe toxicity and do not address the underlying viral drivers of oncogenesis. The purpose of this project is to design and test siRNAs to silence Epstein-Barr Virus' latent and lytic genes in Burkitt's Lymphoma (BL) and computationally query lipid-nanoparticle formulation for targeted delivery. Using gene alignment, three novel siRNA sequences were designed to target specific EBV genes: BZLF1, EBNA1, and LMP2A. Each designed sequence was conserved between EBV strains that circulate worldwide. For in vitro testing, lytic reactivation was quantified in EBV-positive BL and an siRNA designed against BZLF1 was evaluated. In silico interrogation confirmed that the designed siRNA had no off-target effects and had the best stability and binding efficiency of all candidates. While further work is needed, in vitro testing showed modest reduction in lytic gene expression upon delivery of the BZLF1 siRNA to EBV-positive BL cells. Taking the next step, a lipid-nanoparticle atlas was queried to interrogate appropriate formulations for targeted delivery of siRNAs to BL tumors. Through this in silico analysis, the most optimal formulation for the lymph node was 113-O12B (ionizable), DMG-PEG2000 (peg), Cholesterol (sterol), DOPE (helper). Taken together, this project explores the feasibility of siRNA-mediated gene silencing for EBV-driven Burkitt's Lymphoma as well as potential delivery methods for siRNA-based therapies for these cancers.

Awards Won:
Third Award of $1,200