Weill Cornell Medicine

Repurposing of Reverse Transcriptase Inhibitors to Alleviate TLR5-mediated Inflammation in Cystic Fibrosis

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Background & Unmet Need

- Cystic fibrosis (CF) is a genetic disorder caused by mutations in the CF transmembrane conductance regulator (CTFR) gene
- This hereditary mutation results in inadequate mucus production and compromises bacterial clearance mechanisms, predisposing CF patients to persistent lung infections
- To fight bacterial infections, cells express TLR5 in response to bacterial motor protein Flagellum (FLA), which causes an innate immune response
- Unregulated TLR5 activation in response FLA results in pathogenic inflammation
- Most notably, *P. aeruginosa* can cause a life-threatening infection in the pulmonary tract of CF patients by triggering excess TLR5-mediated inflammation
- **Unmet Need:** Anti-inflammatory therapy targeting TLR5 to provide therapeutic relief that does not drive immunotoxicity

Technology Overview

- **The Technology:** Repurposed reverse transcriptase inhibitors (RTis) to alleviate TLR5-driven inflammation in severe cystic fibrosis
- **The Discovery:** Expression of endogenous retroelements is significantly altered in the peripheral blood mononuclear cells (PBMCs) of CF patients
- Flagellum (FLA) delivery results in signaling through TLR5, affecting endogenous retroelements (EREs) downstream
- Reverse transcriptase inhibitors (RTis) selectively inhibit TLR5-induced immunity through expression of TEs
- **PoC Data:** Four RTis inhibited endogenous reverse transcriptase activity and the resulting TLR5-induced inflammatory response in response to FLA, including inflammatory cytokines TNFa and IL-1B
- RTis inhibited TNFa production at all concentrations tested (0.025uM-2.5 uM), and IL-1B at the highest concentration (2.5 uM)

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Patents:
Provisional Filed

Publications:
Dopkins et al. *mBio.* 2023.

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Technology Applications

- Repurposed RTis to alleviate inflammation induced by TLR5 activation in Cystic Fibrosis
- RTis may be used as a cotreatment to alleviate TNF-driven inflammation in sepsis with *S. typhi* or *P. aeruginosa*

Technology Advantages

- RTis circumvent increasing antibiotic resistance in *P. aeruginosa* infection
- RTis bypass inter-individual heterogeneity and immunotoxicity
- Safety and dosages for RTis have been established for individuals on PrEP and people living with HIV
- Production of RTis in commercial quantities has been established by several manufacturers

Supporting Data / Figures

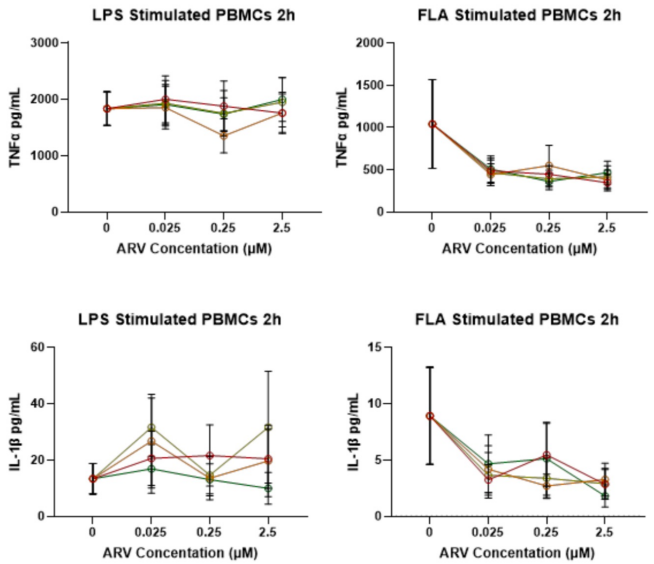

Figure 1: RTi delivery inhibits cytokine production in response to acute TLR5 activation.

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