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 (CFTR) 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) |

## Inventors:
- Nicholas Dopkins
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## Patents:
- Provisional Filed

## Publications:

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## Cornell Reference:
- D-10455
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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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