DEVELOPMENT OF QRM-003, A NOVEL NEBULIZED ANTIBIOTIC FOR THE TREATMENT OF NONTUBERCULOUS MYCOBACTERIAL INFECTIONS IN CYSTIC FIBROSIS

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Introduction

Nontuberculous mycobacteria (NTM) infection is an emerging threat to cystic fibrosis patients1-3. NTM infection reduces lung function, survival4-5, and treatment strategies involve long, intensive, systemic antibiotic regimens, often involving toxicity/adverse drug reactions6-7.

Purpose: To develop a novel, aerosolized therapeutic for the treatment of NTM infections in CF patients.

Hypothesis

QRM-003 is tolerable, and is effective at reducing bacterial infection in models of NTM infection

Materials

QRM-003 (Clofazimine inhalation suspension)

- **API Concentration**: 19 mg/ml
- **pH**: 6.5
- **Osmolality**: 310 mOsm/kg
- **Suspension Particle Size**: D50 = 0.6 µm, D90 = 1.2 µm

Methods

Objective 1: Cell Viability and Macrophage Uptake

- Epithelial cells were exposed to QRM-003 (19 mg/ml) via Vitrocell for up to seven days under conditions to mimic the air-liquid interface.
- Acridine-orange and CLSM was used to determine cell viability.
- QRM-003 was incubated with THP-1 cells for 24 hours.
- Light microscopy was used to determine macrophage uptake of clofazimine crystals.

Objective 2: In vivo Efficacy

- Four mouse models of NTM infection – either acute or chronic, treated Q2D
  - **MABSC/SCID/Acute and MABSC/CFTR/Acute**
    - **MAC/Beige/Acute**
      - 2 Day Infection 15 - 19 Days Treatment
    - **MAC/Beige/Acute**
      - 7 Day Infection 19 Days Treatment
    - **MAC/Beige/Chronic**
      - 28 Day Infection 27 Days Treatment

- Treatments: a) Saline, b) Clofazimine (oral, 20 mg/kg), or c) QRM-003 (IT, 10 mg/kg)

Results

- **Figure 1**: Representative images of cell viability of various pulmonary epithelia after exposure to QRM-003 (1× magnification 40x).
- **Figure 2**: THP-1 cells before incubation with QRM-003 (19 mg/ml).
- **Figure 3**: THP-1 cells after 24h of incubation and washing procedure with QRM-003 (both magnification 40x). Green/orange = live cells, red = dead cells.
- **Figure 4**: Bacterial recovery from lung tissue following various infection models. *p<0.05 vs. Saline (control). n=5-6.

Conclusions

- QRM-003 was generally well tolerated across all time-points and pulmonary epithelial cells investigated.
- Clofazimine from QRM-003 maintains the ability to be taken-up by a macrophage cell line – this is important for activity against intracellular NTM infection.
- QRM-003 demonstrated the greatest antimycobacterial activity against both *M. avium* and *M. abscessus* in all models investigated.
- This increased activity was significantly improved compared to oral administration of clofazimine.

Discussion

- Qrumpharma has developed the first inhalation suspension of clofazimine suitable for nebulized administration.
- QRM-003 has demonstrated tolerability, and potent antimicrobial activity in various *in vivo* NTM infection models.
- This activity is significantly improved compared to oral clofazimine.

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References