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

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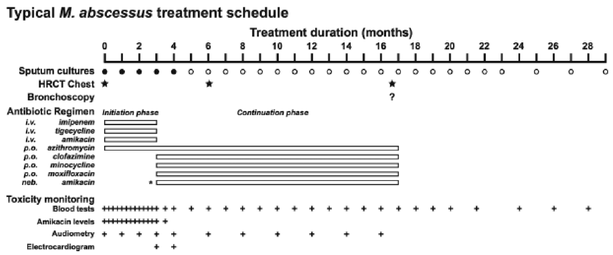
Introduction

Nontuberculous mycobacteria (NTM) infection is an emerging threat to cystic fibrosis patients[1-3].

	2006	2010	2011	2014	2015	2016	2017
Mycobacterial species (% of patients infected)	--	10.1	10.8	12.2	11.9	12.7	13

- NTM infection reduces lung function, survival[4,5].
- Treatment strategies involve long, intensive, systemic antibiotic regimens, often involving toxicity/adverse drug reactions[6,7].



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	D_{50} – 0.6 µm D_{90} – 1.2 µm

Objective 1: Cell Viability and Macrophage Uptake

Methods

- 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.

Results

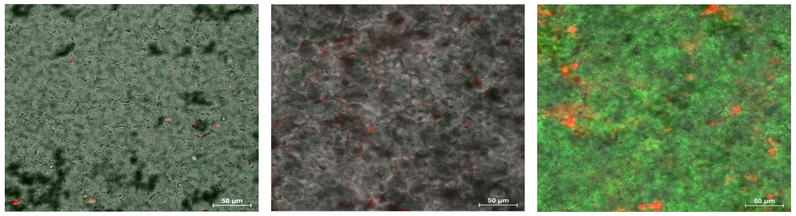


Figure 1: Representative images of cell viability of various pulmonary epithelia after exposure to QRM-003 (19 mg/ml). Green/gray = live cells, red = dead cells. a) hALEVi cells after 5 hour incubation; b) Calu-3 cells after 2 day incubation; c) A549 cells after 7 days.

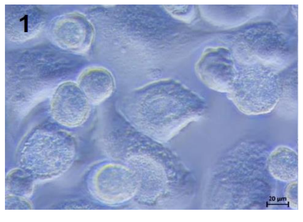


Figure 2: THP-1 cells before incubation with QRM-003. (1: magnification 400x)

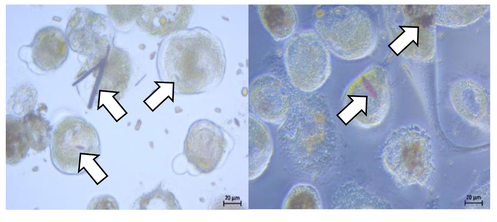


Figure 3: THP-1 cells after 24h of incubation and washing procedure with QRM-003 (both magnification 400x). White arrows – clofazimine crystals

Objective 2: *In vivo* Efficacy

Methods

- Four mouse models of NTM infection – either acute or chronic, treated Q2D

MABSC/SCID/Acute and MABSC/CFTR/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

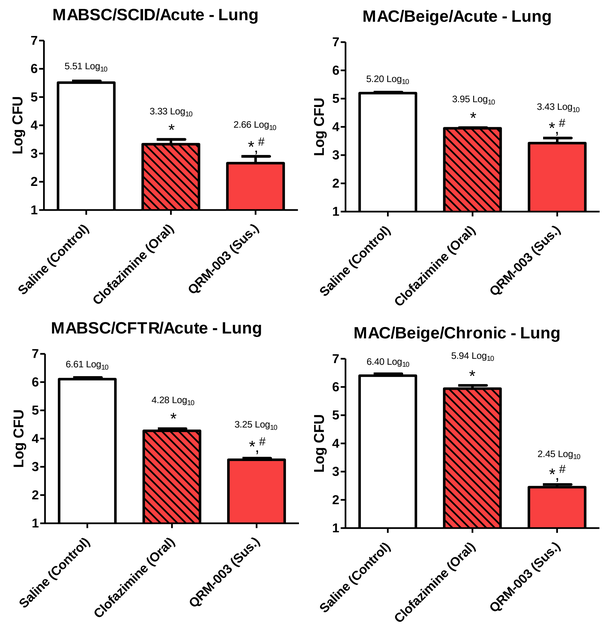


Figure 4: Bacterial recovery from lung tissue following various infection models. *p<0.05 vs. Saline (control); #p<0.05 QRM-003 vs. Clofazimine (Oral). n = 5-6.

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.

Funding

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1. CFF Patient Registry 2015; 2. CFF Patient Registry 2015; 3. CFF Patient Registry 2017 Highlights; 4. Qvist et al., J Cystic Fibrosis 2016; 5. Gommans et al., Respir Med 2015; 6. Floto et al., Thorax 2016; 7. Griffith et al. AJCCRM 2007