The development of nebulized antimycobacterial antibiotics (QRM-003 and QRM-006) for the treatment of nontuberculous mycobacterial infections in cystic fibrosis patients

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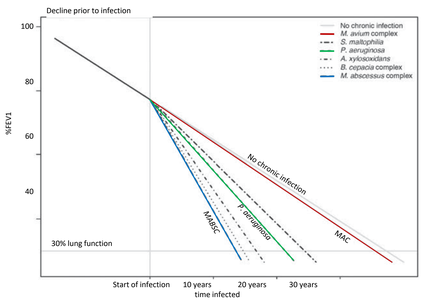
Introduction

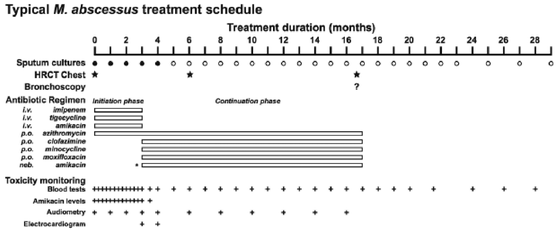
Nontuberculous mycobacteria (NTM) infection is an emerging threat to cystic fibrosis patients

	2000	2005	2010	2014	2015
Mycobacterial species (%)[F]	-	-	10.1	12.2	11.9

Percentage of patients with 1+ mycobacterial species in sputum culture[1]



Effect on lung function of chronic infection from onset to end stage lung disease in Danish CF patients[2]



Typical treatment strategies for both *M. avium* and *M. abscessus* involve prolonged, systemic (i.e. oral or i.v.) intensive antibiotic treatment regimens, which often involve a number of serious side effects/toxicities[3].

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

Hypothesis

The administration of a novel therapeutic in addition to current treatment regimens will improve CF patient outcomes with NTM infection

Objectives

Objective 1 - Performed in collaboration with PharmBioTech GmbH (Saarbrücken, Germany)

To develop a stable formulation of two antibiotics for aerosolized administration

The first objective of development will be the formulation of aqueous drug suspensions to optimize aerosol delivery.

Targeted parameter ranges:

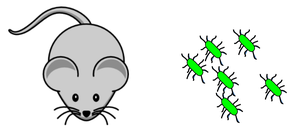
1. Concentration: QRM-003 or QRM-006 may range from 10 to 100mg/mL (depending on suspension and solubility).
2. Acidity: the pH range of the aerosol formulation should be between 5.5 and 7.0. An inert buffer may be added.
3. Osmolality: Between 200 and 700mOsm/kg.
4. The ionic concentration should be between 31 and 300mM of chloride as a permanent anion.
5. The viscosity should be smaller than 1.5cp. Higher viscosities need adaptation of the inhalation device.
6. Sensitivity of aerosol formulation to physical and temperature challenges (Nebulizer Device dependent)
7. Acceptable aersol characteristics (output, MMAD, GSD)

Milestone #1: Identification of aqueous formulations for QRM-003 and QRM-006, and characterization of aerosol properties

Objective 2 – Performed in collaboration with Dr. Diane Ordway

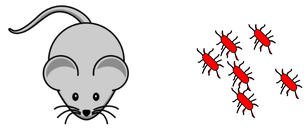
To quantify the in vivo activity of QRM-003 and QRM-006 in mouse models of NTM respiratory infection

Model 1 – QRM-003/006 activity against *M. avium* infection models



Beige Mouse — Low dose aerosol of *M. avium* 2285

Model 2 – QRM-003/006 activity against *M. abscessus* infection models



CFTR$^{-/-}$ Mouse — Low dose aerosol of *M. abscessus* 103

Day 1 – Instillation of bacterial load
Acute model
Day 8 – Daily aerosol treatment of QRM-003/006, or systemic equivalent doses
Day 18 – Quantification of bacterial load

Chronic Model
Day 28 (*M. avium*)/Day 8 (*M. abscessus*) – Daily treatment of QRM-003/006, or systemic equivalent doses
Day 70 (*M. avium*)/Day 35 (*M. abscessus*) - Quantification of bacterial load

Milestone #2: Quantification of QRM-003 and QRM-006 *in vivo* activity against NTM bacteria in CF-relevant setting

Objective 3 – Performed in collaboration with Dr. Veronique Dartois

To assess the distribution of QRM-003 and QRM-006 in lung tissue and circulation after respiratory administration

Lung tissue and serum samples obtained from Objective 2 will be sent for quantification via LCMS and MALDI-MSI analysis

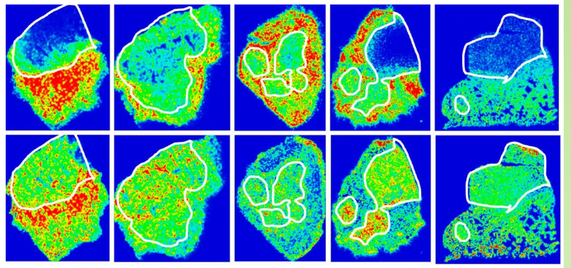


Figure 1, from Prideaux *et al* (2015[14], to exemplify the MALDI-MSI imaging of drug concentrations throughout lung tissue sections.

Milestone #3: Quantification of QRM-003 and QRM-006 localization after *in vivo* aerosol administration

Discussion

NTM infection is a serious, emerging threat to CF patients, and current treatment strategies involve extended courses of multiple concurrent antibiotics.

We hypothesize that the use of QRM-003 or QRM-006 will improve culture conversion rates, reduce duration of antimycobacterial therapy, and improve patient outcomes

1. CFF Patient Registry 2015; 2. Qvist et al, J Cystic Fibrosis 2016; 3. Floto et al, Thorax 2016; 4. Prideaux et al, Nat Med 2015