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.

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 aerosol 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

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

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

Day 28 (M. avium)/Day 35 (M. abscessus) – Daily treatment of QRM-003/006, or systemic equivalent doses

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

Hypothesis

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

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

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