Preclinical efficacy assessment in a mouse model of pulmonary *M. abscessus* infection

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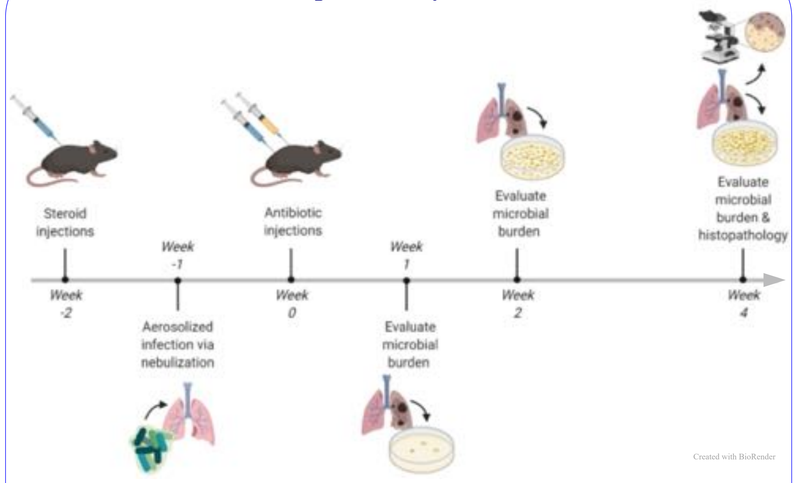
ABSTRACT

Most notable among the nontuberculous mycobacteria (NTM) is *Mycobacteroides abscessus* (*Mab*), an opportunistic environmental pathogen capable of causing chronic pulmonary infections that are often incurable partially due to natural antibiotic resistance. Current treatment recommendations against *Mab* include repurposed regimens often associated with toxicities and side effects; and preclinical investigations remain stagnant largely due to a lack of proven mammalian models for *Mab* pathology. **We developed a mouse model of pulmonary *Mab* infection that allows for pathological investigations in the lungs as well as the evaluation of efficacies of antibiotics.** We provide evidence of sustained proliferation of pulmonary *Mab* evaluated through microbial burden and histopathology of murine lung lesions to enable investigations into the nature of this emerging pathogen. Distinct bacteriostatic and bactericidal responses to different single-drug regimens, including novel antibiotics and synergistic drug pairs, demonstrate the utility of this model for preclinical testing of antimicrobial chemotherapies against *Mab*.

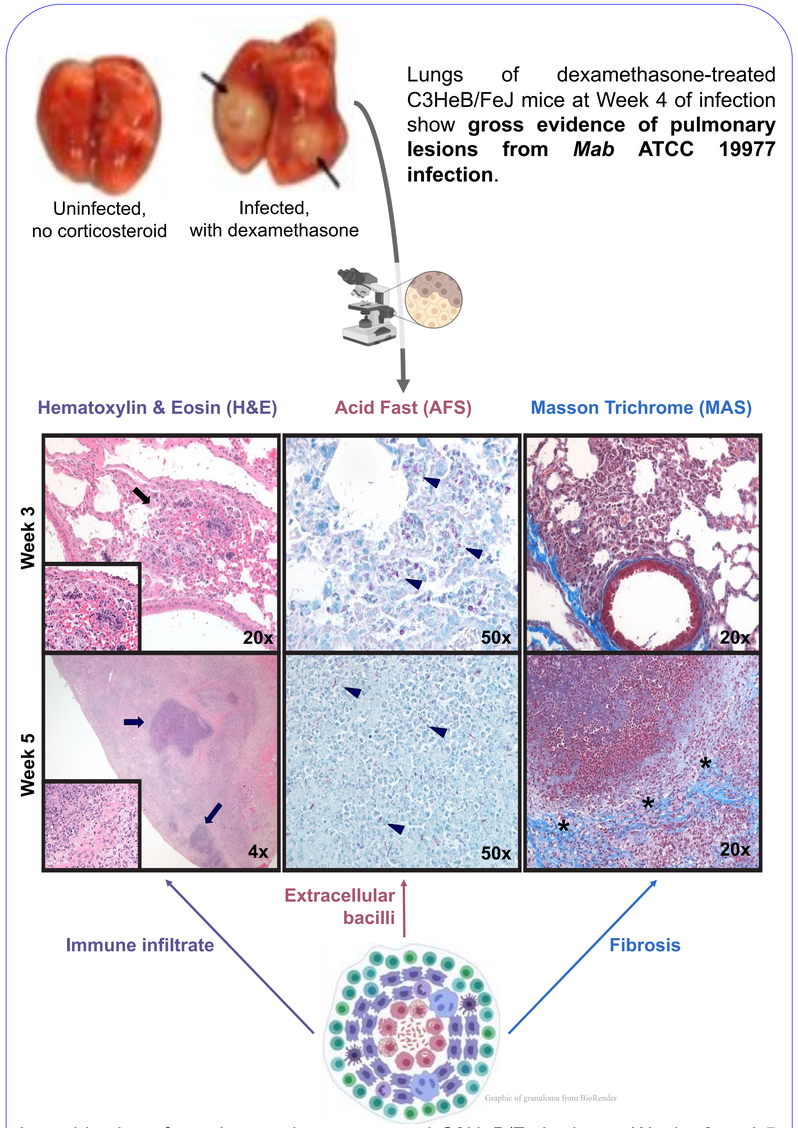
A mouse model of pulmonary *M. abscessus* infection



1. C3HeB/FeJ mice (female, 5-6 weeks old, Jackson Laboratory) treated with dexamethasone (5 mg/kg/day) for one week.
2. Aerosolized *Mab* infection (ATCC 19977 or clinical isolate) via nebulizer with one week stabilization.
3. Antimicrobial chemotherapy begins using human equivalent dosages via subcutaneous injection and/or gavage.
4. Lungs harvested and evaluated for *Mab* histopathology and/or treatment efficacy.

Read more here!
Maggioncalda, Emily C et al. "A mouse model of pulmonary Mycobacteroides abscessus infection." *Scientific reports* vol. 10,1 3690. 28 Feb. 2020, doi:10.1038/s41598-020-60452-1

HISTOPATHOLOGY



Lungs of dexamethasone-treated C3HeB/FeJ mice at Week 4 of infection show **gross evidence of pulmonary lesions from *Mab* ATCC 19977 infection**.

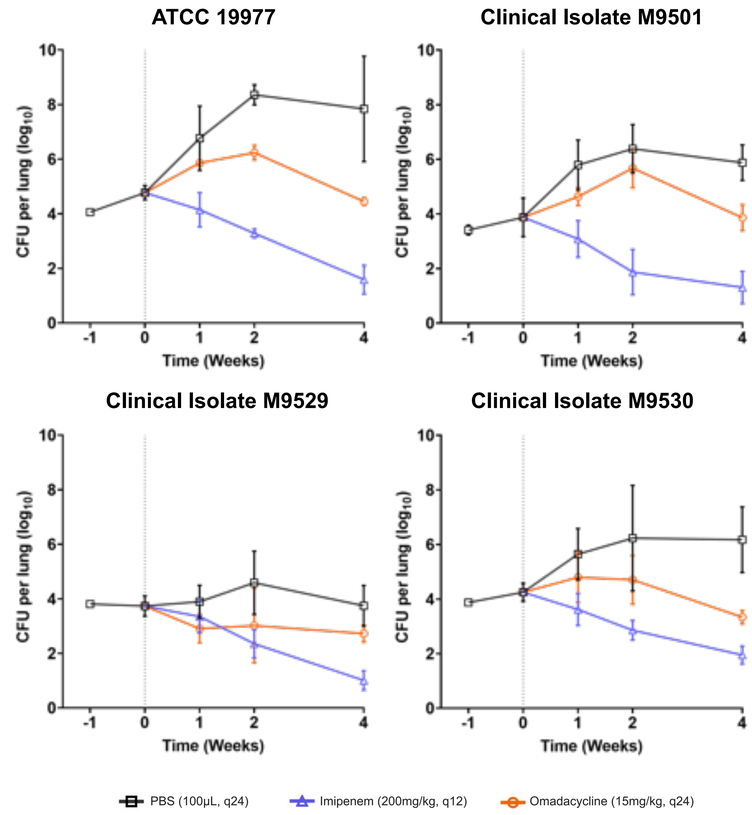
Lung histology from dexamethasone-treated C3HeB/FeJ mice at Weeks 3 and 5 of infection examined with hematoxylin & eosin (H&E; insets at 50x magnification), acid fast (AFS) and Masson Trichrome (MAS) stains respectively show **pulmonary lesions with lymphocytic immune infiltration, extracellular bacilli, and collagen deposition indicative of fibrosis collectively replicating the organized histiocytic granulomas found in human *Mab* pulmonary infection.**

Histopathology of murine lung lesions shows recapitulation of hallmarks of pulmonary *M. abscessus* disease in humans and enables *in vivo* investigations into the nature of this emerging pathogen.

Supported by NIH R21 AI137720 and CFF award LAMICH17GO.

EFFICACY OF OMADACYCLINE

Pulmonary *Mab* infections in C3HeB/FeJ mice show distinct efficacy responses to single-drug regimens by assessing changes in *Mab* burden (CFU per lung). Antibacterial efficacy of bacteriostatic and bactericidal therapies against different *Mab* strains can be differentiated from the untreated control group using this infection model. Treatment group differentiation is also demonstrated by the biphasic bacteriostatic effect of the novel tetracycline derivative, omadacycline, compared to the bactericidal effect on *Mab* of imipenem-treated mice.



Read more here!
Nicklas, Danielle A et al. "Potency of Omadacycline against *Mycobacteroides abscessus* Clinical Isolates *In Vitro* and in a Mouse Model of Pulmonary Infection." *Antimicrobial agents and chemotherapy* vol. 66,1 (2022): e0170421. doi:10.1128/AAC.01704-21

Pulmonary *M. abscessus* burden shows distinct responses to different single-drug regimens and demonstrates preclinical efficacy of antimicrobial chemotherapies against *M. abscessus*.

Supported by Paratek Pharmaceuticals, Inc.

I acknowledge contributions of the following lab members: Elizabeth Story-Roller, Chavis Tabor, Ben Eichelman, Randall Basaraba