# 4th Annual NTM Research Consortium Meeting

November 10th, 2017
Dayton, OR

The 4th annual NTM Research Consortium meeting was a 1-day meeting to discuss the current state of NTM clinical and epidemiological research and to review patient-reported research priorities. Clinical researchers and scientists from leading NTM clinical and research sites presented their latest research findings and proposals in a didactic setting with stimulating discussion of challenges facing NTM researchers and clinicians. The environment provided an opportunity to plan future research collaborations and priorities. The following summary will include: meeting attendees, a review of invited presentations and next steps.

*Attendees: see attached list*

## Invited Presentations

### Epidemiology/Clinical Outcomes

**Rebecca Prevots, NIAID/NIH (Maryland) - *Epidemiology of NTM pulmonary disease in the U.S. and beyond***

Summary: Dr. Prevots presented an update on the U.S. and global landscape of NTM epidemiology. In the U.S. in 2017 there were 11 states that have made NTM reportable. A recent publication describing the pulmonary NTM by species in Hawaii 2005-2013 confirmed MAC had the highest prevalence. She discussed the varied epidemiology of NTM by region of Japan. She also described new results of a study of environmental risk factors for NTM. Watershed and soil factors that are associated with increased NTM disease risk include low clay concentrations and high silt concentrations, while lower manganese and soil pH are protective. Last, Dr. Prevots presented a natural research study on *M. abcessus* antibiotic susceptibility among patients undergoing prolonged antibiotic treatment. *M. abcessus* is the second most common species of NTM in the U.S., is highly antibiotic resistant, and currently has limited treatment options. This study followed patients receiving clarithromycin and amikacin treatment, identifying within-patient changes of antibiotic resistance by correlating gene mutations. Despite high levels of exposure to amikacin, only 1 of 16 patients developed resistance to amikacin; clinical, radiographic and microbiologic disease markers indicated progression.

**Ted Marras, University of Toronto (Ontario) - *NTM-PD in Ontario: Practice Patterns and Health Care Costs***

Summary: Dr. Marras presented an overview of Canadian health system and geo-social factors for context of population based study in Ontario Linked public health laboratory with national medical database for entire population of Canada. He noted prior study limitations have included a lack adequate clinical/radiological data to define NTM pulmonary disease (PD) and drug data only available for ages ≥ 65 yrs. Dr. Marras also presented an international comparison of treatment patterns for Pulmonary NTM based on a wide net random sampling of MDs in the EU and Japan. The eligible NTM cases in EU totaled 1012, with 79.4% MAC cases; the eligible NTM cases in Japan totaled 417, with 85.1% MAC cases. Treatment patterns in Japan were overwhelmingly macrolide use. He modeled this study style for a similar analysis of newly incident NTM-PD cases in Ontario in a prospective, population-based cohort. Analysis included those with microbiologic criteria for MAC-PD and M. xenopi-PD, and

described information on resistance, age, single vs. multi-drug treatment, and number of treatment switches (with initial treatment ≥ 60 days).

**Emily Henkle, OHSU (Oregon) - *Extrapulmonary NTM disease in the U.S. and beyond***
Summary: Dr. Henkle defined extrapulmonary nontuberculous mycobacteria infections by exclusion of lower respiratory samples and exclusion of cultures positive for *M. tuberculosis, M. gordonae,* and *M. leprae*. She described 334 Oregon extrapulmonary isolates from 2007-2012, both by disease site, demographics, and species distribution and followed with a similar comparison for North Carolina. She recommends standardizing laboratory testing and reporting, quantifying risks in immunosuppressed and immunocompromised patients, confirming *M. gordonae* as non-pathogenic, and understanding the global epidemiology of NTM.

## Microbiology/immunology updates

**David Lewinsohn, OHSU (Oregon) - *MAIT cells and biomarkers in tuberculosis***
Summary: Dr. Lewinsohn explained Mait cells and T cells and their function as biomarkers of active TB evaluation. His presentation focused on how the evaluation of T cell biomarkers in TB could be useful in the diagnosing NTM.

**Luis Bermudez, OSU (Oregon) - *Mouse models for tuberculous and NTM therapeutic discovery***
Summary: Dr. Bermudez presented on understanding the pathophysiology of populations at risk of NTM infections, and related this to treatment and prevention. When infections are treated with a regimen of antibiotics, the "persister" sub-population remain unaffected by the antimicrobial, allowing growth and recurrent infection rates after treatment regimen ends. This was explored with both amikacin and clarithromycin treatment.

## Building capacity: "Centers of Excellence"

**Timothy Aksamit, Mayo Clinic/BRR (Minnesota) - *Updates in clinical trials for non-cystic fibrosis bronchiectasis: outcomes and design***
Summary: Bronchiectasis is a poorly studied disease, with no current FDA approved inhaled antibiotics for NCFB bronchiectasis. Dr. Aksamit presented conclusions from prior antibiotic trials for bronchiectasis. Clinical phenotypic responses of (non-cystic fibrosis) bronchiectasis patients to inhaled antibiotics are complex. Despite primary endpoints not being met, consistent positive trends have been observed across all phase III studies involving use of inhaled antibiotics for (non-cystic fibrosis) bronchiectasis patients. Inhaled antibiotics as a treatment for bronchiectasis have been safe and well tolerated.

## Future research priorities/Next Steps

**Attendees identified several priorities and next steps:**

1. The NTM Research Consortium will begin enrollment in the FDA-sponsored clofazimine clinical trial, implement the PCORI pragmatic trial if awarded, and target NIH grants in 2018.
2. Formation of a national NTM Clinical Trials Network. Since NTM is a rare disease, there should be a coordinated effort to prioritize and limit competing clinical trials. The PCORI pragmatic trial would be a first step to creating such a coordinated network with an academic coordinating center.

3. Biorepositories are in existence at NTMRC sites, with some overlap in the types of samples that are being stored. Sites currently collect mycobacterial isolates, BAL fluid, serum, plasma, PBMCs, and RNA. Funding for a collaborative registry would allow for standardization of sample and data collection.
4. Publication of the updated ATS/IDSA treatment guidelines is anticipated in 2018; these should be widely distributed to improve adherence to guidelines.
5. Support the formation of an FDA advisory board for NTM therapy.