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NTM-TB INSIGHTS

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Colorado Cystic Fibrosis Research and Development Program Overview

As the cystic fibrosis (CF) population ages, nontuberculous mycobacteria (NTM) are cultured with increasing frequency. NTMs infection can cause progressive lung disease and sometimes rapid decline in lung function. NTM pulmonary disease has long been recognized as a particularly ominous co-morbidity of CF due to uncertainly in diagnosis, the need for prolonged multi-drug treatment regimens with associated drug-related toxicities and unpredictable rates of response. However, the need to address this issue has taken on unexpected urgency, as there is mounting data that various subspecies of *Mycobacterium abscessus* can be transmitted between patients within CF Centers, and this transmission has been associated with devastating clinical consequence. A coordinated effort is required to respond to this looming challenge. In 2015, the Colorado Research and Development Program (Colorado-RDP) was funded by the CF Foundation for the purpose of advancing research in the diagnosis and treatment of NTM in the CF airway. The Colorado-RDP is primarily designed to provide core resources and support for scientists and clinicians in the field, both in Colorado and nationwide. The Administrative Core is directed by Jerry Nick, MD, National Jewish Health and the Co-Director is Scott Sagel, MD, Children's Hospital Colorado There are three research cores. A **NTM Culture, Biorepository, and Coordinating Core** (Director: Charles Daley, MD, Co-Director Max Salfinger, MD) provides state-of-the-art support for culture, basic molecular identification, antimicrobial susceptibility analysis, as well as banking of isolates, and data coordination with CF Centers. All samples received are then forwarded to the **Molecular Core** (Michael Strong, PhD), which provides genomic "fingerprinting" of NTM isolates through whole genome sequencing, to identify isolates which are highly similar between two or more patients, either from patient-to-patient transmission within CF Care Centers, or originating from a common environmental source. A **Clinical Research Core** (Stacy Martiniano, MD, and Jerry Nick, MD) supports the conduct of current and planned clinical trials of NTM diagnosis and treatment and provides data to qualified researchers. Currently, three clinical trials are underway to validate diagnosis and treatment protocols for NTM disease, and to test the pharmacokinetics of oral NTM medications in individuals with CF. All cores are designated as National Cores, allowing access to isolates and data to qualified CF researchers and clinicians nationwide. A **Research Training and Educational Enrichment Program** (RTEEP; Scott Sagel, MD) serves to increase collaboration, education and mentoring between investigators and Cores, and a **Pilot Grant Program** (Brian Day, PhD) funds and oversees translational research proposals on an annual basis, which utilize core resources.

The Colorado-RDP capitalizes on two important resources. The Colorado CF Center is the largest in the United States, and National Jewish Health is home to the largest NTM program in the United States, including the Mycobacteriology and the Pharmacokinetic Laboratories. A research base comprised of 41 Investigators from five affiliated institutions is currently working with the Colorado-RDP, and our goal is to continue to increase the number and breadth of collaborations. The operation and productivity of the Colorado-RDP is reviewed annually by the CF Foundation and an Internal and External Advisory Committee which meets annually.

Jerry Nick, MD, Adult Cystic Fibrosis Program, National Jewish Health, Denver, CO

NTM Culture, Biorepository, and Coordinating Core

The Mycobacteriology Laboratory at National Jewish Health is a national reference laboratory specializing in the growth detection, identification, and antimicrobial susceptibility testing of NTM. National Jewish Health is now supported by the Cystic Fibrosis Foundation (CFF) to bank and further characterize all CF NTM isolates nationwide through complimentary whole genome sequencing (WGS). These isolates are made available to all qualified investigators as a resource for continued research among the CF population. All CF NTM specimens are cultured and isolated for purity to be frozen using flash freeze methodology and stored at -80°C. An IRB-approved Biorepository database has been constructed to gather all documentation of the CF NTM isolates, including: culture and patient information; identification; antimicrobial susceptibility testing (dependent on each submitter's clinical requests); geographical location; and WGS results. Pure genomic DNA of single isolated colonies is extracted from all CF NTM isolates and proceeds forward to the Molecular Core of the Colorado-RDP for WGS.

To date, the Mycobacteriology Laboratory at National Jewish Health has obtained more than 500 CF NTM isolates since January 2016.

Max Salfinger, MD, Mycobacteriology and Pharmacokinetics Laboratory, Charles L. Daley, MD, Division of Mycobacterial and Respiratory Infections, Rachael R. Rodger, MPH, Mycobacteriology Laboratory, Colorado Cystic Fibrosis Research and Development Program, National Jewish Health, Denver, Colorado

Molecular and Genomics Core: Pathogen Surveillance and Characterization using Whole Genome Sequencing

In the Colorado-RDP Molecular and Genomics Core (7), we utilize cutting-edge molecular and genomic methodologies to better understand and characterize NTM lung pathogens. Specifically, we apply methods of next generation DNA sequencing, to rapidly and robustly elucidate the whole genome sequencing (WGS) of NTM pathogens (8) that are infecting individuals with CF. WGS allows us to thoroughly characterize and compare the genetic blueprint of infecting NTM, with a much finer resolution than culture based methods, or single gene speciation. WGS also helps us garner a better understanding of the prevalence, dominance, and diversity of NTM pathogens affecting the CF community. Through this genomic research we aim to elucidate improved molecular biomarkers to help diagnose NTM infections early and accurately. We also utilize WGS in conjunction with phenotypic and computationally inferred information (9) to identify genomic features that may influence pathogenicity, drug resistance and environmental survival. Together these goals are aimed at providing improved tools for clinicians and diagnosticians to recognize, characterize, and treat NTM infections.

The genomic information we generate also is used for infectious disease surveillance. Although most NTM infections are thought to originate from the environment, including the indoor environment, it has been suggested that in some cases certain NTM species may be able to be transmitted person to person (10). As such, we have implemented robust and precise genomic pipelines for comparative analysis of NTM genomes. This approach allows us to quickly identify genetically similar strains that may originate from a shared environmental exposure or may have been transmitted from person to person. We also use these methods to investigate strains associated with potential outbreaks. Once all results from the Molecular Core are available, a report will be issued by the Mycobacteriology Laboratory.

To date we have sequenced hundreds of NTM genomes, and plan to sequence more than 1,000 genomes over the next three years. As we expand our understanding of the genomic and phenotypic features of NTM, we hope to provide

useful resources to health care providers treating patients with NTM disease, researchers interested in NTM, and to CF clinics and clinicians, to aid the diagnosis and treatment of NTM infections relevant to CF.

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Michael Strong, PhD, Nabeeh A. Hasan, PhD, L. Elaine Epperson, PhD, Center for Genes, Environment, and Health, National Jewish Health, Denver, Colorado

Clinical Core

The Clinical Research Core supports RDP investigators in all aspects of clinical and translational research related to NTM infection in CF. This includes assistance with study design, and implementation of trials through help with study coordination, screening, recruitment, biostatistical and bioinformatics support. Resources are available to collect, store and distribute data and samples, with a particular focus on biomarker development. The Clinical Research Core is currently supporting three ongoing NTM trials at our Center:

- Prospective Evaluation of NTM Disease in Cystic Fibrosis (PREDICT Trial): Isolation of NTM from CF sputum is relatively common, and of uncertain significance, as clinical sequelae can range from undetectable to severe. In the context of CF, the diagnosis of NTM disease and the decision to treat currently requires more than one positive culture accompanied by evidence of accelerated clinical decline. Achieving a standardized diagnosis of NTM disease is essential for the conduct of therapeutic trials. The primary objective of this trial is to develop and test feasibility of a standardized diagnostic protocol to assist with identification of CF patients requiring treatment for NTM. All NTM isolates recovered from patients on the trial are banked through the Culture and Biorepository Core, and undergo WGS through the Molecular Core.
- Prospective Algorithm for Treatment of NTM in Cystic Fibrosis (PATIENCE Trial): No NTM treatment protocol has been validated in the setting of CF. This primary objective of this trial is to develop and test the feasibility of a standardized treatment algorithm for confirmed disease by either *Mycobacteria avium* complex (MAC) or *Mycobacteria abscessus* including its three subspecies. As with the PREDICT Trial, all isolates are banked and undergo whole genome sequencing.

• A pharmacokinetic trial of oral agents for the treatment of NTM in CF: NTM pulmonary infections are difficult to treat and treatment failure is common in CF, likely due in part to sub-therapeutic drug levels. The purpose of this study is to determine oral antimycobacterial drug pharmacokinetics and pharmacodynamics in patients with CF. Upon completion of this study we will determine if and how the PK of antimycobacterial drugs are altered in CF. More importantly, we will develop CF-specific guidelines to achieve therapeutic goals with recommendations for drug dosing, enzyme use, and timing of therapeutic monitoring to be used for future treatment of NTM lung disease in CF.

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Stacey Martiniano, MD, Department of Pediatrics, University of Colorado School of Medicine, Children's Hospital Colorado, Aurora, CO; Jerry Nick, MD, Adult Cystic Fibrosis Program, National Jewish Health, Denver, CO

Colorado CF Research Training and Educational Enrichment Program

The Colorado CF Research Training and Educational Enrichment Program (RTEEP), is a key component of the Colorado-RDP. The RTEEP provides training of post-doctoral fellows, junior faculty, early-stage investigators, and established investigators new to CF in the diagnosis and management of NTM lung infections. In the Colorado-RDP Program, trainees gain skills necessary for diagnosing NTM infection, including exposure to state-of-the-art mycobacterial and molecular diagnostic testing, phenotyping of NTM disease, experience with biospecimen collection and biomarker assessment, as well as involvement in a collaborative interdisciplinary Program. *Our overall goal is to provide trainees within the Colorado RTEEP with the professional and research skills to lead sustained and productive academic research careers in CF and NTM infections.*

Training in the Molecular Core under the direction of Dr. Michael Strong has been a central focus of the RTEEP. Several post-doctoral fellows and junior faculty members have been learning and performing state-of-the-art molecular biology and computational methods for characterization and identification of NTM species. These methods include laboratory training in complete genome sequencing, microbiome characterization, transcriptome analysis, and targeted gene sequencing. These individuals have been implementing high throughput molecular and computational methodologies in order to examine the bacterial constituents of clinical samples using next generation sequencing, phylogenomic analysis to identify and monitor potential clonal strains, and are receiving instruction in bioinformatics and biostatistics for the analysis of molecular NTM data.

We host a monthly Colorado-RDP Research in Progress ("RIP") seminar to improve interdisciplinary collaborations and to provide a regular forum for the CF research community to advise the Core Principle Investigators as to strengths and weakness of available services and how current services can be improved. All Center faculty, fellows, and other trainees are invited to participate.

We helped to plan and participated in two conferences in 2016: the ***Colorado Mycobacterial Conference***, held in Ft. Collins Colorado in June (http://mycobacteria2016.org/meeting-agenda/) and the ***2016 North American Cystic Fibrosis Conference (NACFC)*** in October in Orlando, Florida (https://www.cff.org/Our-Research/North-American-CF-Conference/2016-NACFC/). Drs. Strong and Stacey Martiniano gave invited lectures at the Colorado Mycobacterial Conference and trainees presented abstracts. Members of the Colorado-RDP also are involved in a NACFC Symposium

session entitled, *"Non-tuberculous Mycobacteria: Now That the Guidelines Are Published"*. Dr. Martiniano is co-chairing this Symposium along with Dr. Moira Aitken (University of Washington, Seattle).

Scott Sagel, MD, PhD, Department of Pediatrics, University of Colorado School of Medicine, Children's Hospital Colorado, Aurora, CO

Recent Staff Publications

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Meetings/Conferences/Lectures

The 54th Annual Denver TB Course April 5-8, 2017; Molly Blank Conference Center at National Jewish Health Main Campus. For more information and registration: **https://www.nationaljewish.org/tbcourse2017**

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