

## The “Uber-Bugs”: Tackling NTM Lung Disease at CDI

There is a pernicious disease, called NTM (Non-Tuberculous Mycobacteria), that can be contracted by inhaling naturally occurring organisms from soil and water. NTM bacteria can be found almost anywhere, including lawn soil and your showerhead. Once inside, the organisms can infect the lungs and airways and can lead to coughing, fatigue, weight loss - and lung damage. In many patients, the disease can become progressive and increasingly debilitating. It is difficult to cure and in some cases, incurable. Yet, Dr. Dick and his team at CDI are making headway in their multi-front war against it.

### Cause for Alarm

There is an urgent medical need to find new drugs for people with NTM disease. Currently, the available treatment involves the long-term use of antibiotics, which carry their own side effects, are often not effective to begin with, and can become more and more inefficient over time. Many patients take these antibiotics over the course of years, often without improvement.

Cause for concern is the climbing rate of NTM infections worldwide. While some people may become exposed to NTM and not experience any resulting infection, others, who are more susceptible, do become infected and symptomatic. There is speculation that the increasing rate can be attributable to the greater proportion of elderly people in the population today, since they are more vulnerable to this type of lung infection. Other vulnerable groups include patients with COPD, cystic fibrosis, those who have had organ transplants, and other immunosuppressed patients.

### CDI's Role

Dr. Dick has 20 years of experience in antibacterial drug discovery and R&D program management and is one of the newest recruits to CDI. One of the primary objectives of his lab is to find new drugs against NTM bacteria. To that end, he has recently published three articles that highlight different elements of his lab's approach.

### *Plans for the \$33M CDI Anti-infectives Program: Using Something that Works to Make Something Great*

Dr. Dick's first article, with Dr. Ganapathy as lead author, is entitled “Repositioning rifamycins for *Mycobacterium abscessus* lung disease”. It was published in ‘Expert Opinion on Drug Discovery’ (<https://doi.org/10.1080/17460441.2019.1629414>) and presents a comprehensive review on rifamycins in the context of NTM lung disease. The paper describes one of the strategies the lab is employing to address NTM disease with a focus on an incurable form of NTM, *M. abscessus*. The authors propose that one of the reasons why it is yet incurable is because a key drug that is used successfully against Tuberculosis and some NTMs (since they are relatives of the Tuberculosis bacillus) doesn't work on *M. abscessus*. However, recently Dr. Dick and his team identified an analog, or a drug with a similar structure, that has shown promise. Now that it has been demonstrated, that that molecule class works, Dr. Dick's group plans to ‘reposition’ that

drug, i.e. make a better, more potent version that could be used in fighting various forms of NTM, including the incurable *M. abscessus*. This NTM drug discovery project is part of a comprehensive NIH-funded program aiming for the development of anti-infectives and was recently initiated at CDI under the leadership of Dr. Perlin.

#### *Rethinking a Common NTM Treatment Regimen*

Dr. Dick's second article, with Ms. Lindman as lead author and entitled "Bedaquiline eliminates bactericidal activity of imipenem and cefoxitin against *Mycobacterium abscessus*", was published in 'Antimicrobial Agents and Chemotherapy' (<https://doi.org/10.1128/AAC.00827-19>). The paper describes their finding that there is potentially a problem to co-administer bedaquiline and beta-lactam antibiotics to treat *M. abscessus* NTM disease. The authors uncovered that adding the new drug bedaquiline to a treatment regimen containing beta lactams may impair the ability of the beta lactams to kill the targeted bacteria. Thus, the authors question an often-used practice of combining these two antibiotics to treat NTM disease. They then underscore the need to explore this further in animal models. If this finding is confirmed in animal models, it has major implications for clinical practice: giving more drugs may not always be better.

#### *Raising Awareness and Stimulating NTM Research*

Dr. Dick's third article, with Dr. Dartois (CDI) and Dr. Sizemore (NIH) as co-authors, entitled "NTM—The New Uber-Bugs", is an editorial for an NTM-focused special issue in 'Frontiers in Microbiology' (<https://doi.org/10.3389/fmicb.2019.01299>). In this Research Topic, consisting of 24 articles, 130 globally leading NTM researchers present an overview of the current state of NTM research. They also identify gaps and give directions for future research. Dr. Dick and his colleagues initiated and edited this article collection to generate awareness and stimulate research in the NTM space.