Innovations
UNIVERSITY OF COLORADO
ANSCHUTZ MEDICAL CAMPUS

Pre-Ribosomal RNA Biomarkers for Tuberculosis Treatment Response

Category

Mycobacterium Diagnostic

Problem

Current mycobacterial infection markers of treatment efficacy cannot accurately predict failure and relapse

Technology Overview

A precursor-rRNA marker for treatment response in patients with mycobacterial infections

IP Status

- Patent Pending
- Available for Exclusive or Non-Exclusive Licensing

Advantages

- Accurate, early marker for treatment response
- Can be used to identify relapse risk
- Could be applied to other chronic bacterial infections

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Problem: Diseases caused by mycobacteria are a leading cause of death worldwide. Mycobacteria are broadly divided into *Mycobacterium tuberculosis* (Mtb) and non-tuberculous mycobacteria (NTM). Mtb causes tuberculosis (TB), which kills 1.5 million people each year. NTM comprise over 125 species, and in the U.S. are a more common cause of disease than TB. Even with adherence to months or years of multiple, often toxic, antibiotics, patients with mycobacterial infections may fail treatment or relapse. Drug development and individual patient care is impeded by a lack of accurate surrogate markers of treatment response. Treatment failure and relapse are often caused by sub-populations of "persister" bacteria that survive early bactericidal killing. Existing culture-based markers of treatment efficacy fail to accurately predict failure and relapse, likely because they reflect the number of bacteria killed in the early bactericidal phase rather than in the subsequent sterilizing phase of treatment. Development of an accurate surrogate marker of treatment effectiveness would have a profound effect on drug development and clinical practice.

Solution: A group of researchers led by Dr. Nicholas Walter have discovered that the ratio of precursor-rRNA (pre-rRNA) to total 23S rRNA can be used as an accurate, early biomarker of treatment response in patients with mycobacterial infections. The pre-rRNA/23S ratio indicates the rate of ongoing rRNA synthesis, and can be used to successfully monitor "pesisters" during the sterilizing phase. They found that this ratio decreased in cultured Mtb and Mtb from the lungs of mouse models of TB after treatment with sterilizing antibiotics. In contrast, treatment with antibiotics with high bactericidal activity but low sterilizing activity had a minimal impact on the ratio. They also showed that in human sputum standard TB treatment suppressed the Mtb pre-rRNA/23S ratio, as shown in Figure 1.

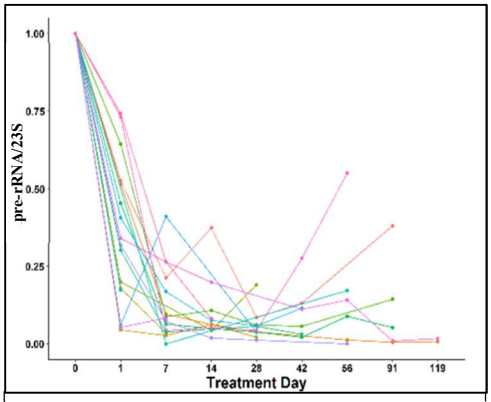

Figure 1: Change in pre-rRNA/23S in sputum during treatment of Vietnamese patients. Colored lines represent individual patient values (scaled to the same baseline value for clarity).

Advantages and Value Propositions: Existing mycobacterial culture-based markers provide imprecise, poorly predictive information with minimal statistical power. The diagnostic described here can be used for monitoring drug efficacy or identifying relapse risk in patients infected with mycobacteria and has the potential to be used to monitor other chronic bacterial infections. There are tests on the market being developed that are used to predict a patient's initial response to treatment or identify specific drug resistance, but there are none that can be used early in treatment to assess the overall impact of a therapy on ultimate cure.

Additional Documents and Sources:

"Methods of Measuring Treatment Efficacy in Mycobacterial Diseases." Provisional Patent No. 62/534,487 filed July 19, 2017.

Walter N, Dolganoc G, Garcia B, Worodria W, Andama A, Mususu E. Transcriptional Adaptation of Drug-Tolerant *Mycobacterium Tuberculosis* During Treatment of Human Tuberculosis. *Journal of Infectious Diseases.* 2015;212(6):990-998.

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