Application of multiplexed ion mobility spectrometry towards the identification of host response protein signatures of treatment of pulmonary tuberculosis

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Introduction

Tuberculosis (TB) is one of the leading causes of deaths from infectious diseases.

According to WHO, 1/3 of world’s population has TB infection.

In 2015, 10.4 million near TB cases with 1.4 million deaths were reported worldwide.

Microscopy and culture are the current gold standards for diagnosing and monitoring disease.

However, these methods suffer from low specificity and sensitivity; prompting efforts to identify new quantitative, non-antibody based TB biomarkers.

A blood-based protein signature could hold the promise to improve the efficiency and predictive accuracy of monitoring treatment response.

Methods

289 participants enrolled from clinical trials sites in North America, South America, Uganda, Spain, Brazil, Peru, and Vietnam

Participants had sputum smear positive for acid fast bacilli at baseline, and were culture positive for drug-susceptible pulmonary TB

Serum was collected, processed and stored at baseline (time of enrollment), and after 8 weeks (end of study).

Serum samples were depleted of 14 highly abundant proteins using a mixed TOF MS column.

A 60-min gradient was used with the IM-MS platform and data was collected from 100-3200 m/z.

Identification and quantification of the detected peptide peaks was performed utilizing the Accurate Mass and Time (AMT) tag approach.

Conclusions

- 876 unique proteins were identified using multidimensional capabilities of LC-IM-MS
- A comprehensive correlative study was performed ranking all relevant clinical and indicators with the respective serum protein at both week 0 and week 8 time points, where the most significant ones include visit, enrollment region, cough, and BMI
- Correlation of protein marker with clinical efficacy measurements identified 188 proteins representing candidates for blood-based signatures
- Top KEGG pathway, coagulation and complement cascade, mapped 34 proteins including both up and down regulation, focusing on coagulation prevention or promoting dissolution of fibrin clots with additional protein classes including acute phase markers, defense proteins, lipid transport and metabolism.

Results

1) Correlation of global protein values with clinical variables

- Top KEGG pathway, coagulation and compliment cascade,
- Correlation of protein marker with clinical efficacy

References


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Career Opportunities: http://omics.pnl.gov/careers

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