SCRIPT – Successful Clinical Response In Pneumonia Therapy

Abstract

This innovative integrated systems biology application seeks to delineate the complex host/pathogen interactions occurring at the alveolar level that lead to unsuccessful response to therapy in serious pneumonia. To achieve this objective, we will leverage our unique access to alveolar fluid collected as part of routine clinical care in mechanically ventilated patients with suspected pneumonia in our medical intensive care unit. Bronchoalveolar lavage fluid will be obtained serially from well characterized mechanically ventilated patients with Pseudomonas or Acinetobacter pneumonia. Both of these CDC- designated serious hazard level pathogens have clinical failure rates as high as 50%. A robust clinical definition will allow comparison of both host and pathogen signatures associated with failure of therapy vs. success. These clinical specimens and extensive patient phenomics will anchor two mutually supportive and iterative research projects. Project One will deploy robust tools for flow sorting macrophage and lymphocyte subset populations, isolating RNA from these populations, and performing transcriptomic and epigenomic analysis to compare successful and unsuccessful host responses to infection. Project Two will focus on both specific pathogen genomic profiles associated with unsuccessful outcome. Changes in microbiome communities will be comprehensively assessed by shotgun deep sequencing to detect bacteriophage, other virus, and fungal DNA, in addition to bacterial. The Technology Core will perform cell sorting of NBBAL macrophage and lymphocyte subsets, RNA sequencing, and whole genome methylation, and perform parallel studies in a unique humanized alveolar macrophage mouse model. A Data Management and Bioinformatics Core will develop tools to reduce the dimensionality of these large comprehensive datasets, including the clinical phenomics, and provide them to the Modeling Core. The Modeling Core will then use innovative modeling approaches including a model of the alveolus during pneumonia as an ecosystem out of balance combined with unique machine learning tools and neural networks to generate biomarkers of host, pathogen and/or microbiome patterns predictive of successful pneumonia outcome. Predictive biomarkers developed in the Modeling Core will then be validated in a prospective confirmatory cohort of patients in whom analogous data will be generated. The Administrative Core will perform the outward-facing role of education and outreach to the community and sponsor, as well as regularly exchanging datasets, analytic tools, and specimens with NIH-sponsored/approved repository sites.

Public Health Relevance

The Successful Clinical Response In Pneumonia Treatment (SCRIPT) systems biology center seeks to delineate the complex host/pathogen interactions occurring at the alveolar level that lead to unsuccessful response to therapy in serious pneumonia. We will leverage our unique access to alveolar fluid collected as part of routine clinical care in mechanically ventilated patients to generate clinical phenomic, transcriptomic, epigenomic and metagenomic data that describe the host response, pathogen characteristics and microbiome of the alveolar space during pneumonia. We will then integrate this comprehensive phenotypic data into an ecosystem-based model to generate predictive biomarkers of pneumonia outcome for subsequent validation in a second cohort and tested for causality in a humanized alveolar macrophage mouse model.

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