

**NUS Graduate School for Integrative Sciences and Engineering
Research Project Write-up**

Title of Project : **Activation and formation of neutrophil extracellular traps in severe influenza and secondary pneumococcal pneumonia**

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Short Description

Patients infected with highly pathogenic influenza viruses (e.g. H5N1) develop signs of acute lung injury (ALI) with pulmonary infiltration and edema, which further progress into acute respiratory distress syndrome (ARDS) and respiratory failure. Mice lacking IL-17RA (necessary for neutrophil recruitment) exhibit decreased morbidity and mortality compared to wild-type mice following influenza virus challenge. Neutrophils play key roles in acute lung injury by producing reactive oxygen intermediates, inflammatory cytokines and enzymes such as elastase, or via formation of neutrophil extracellular traps (NETs), which can cause alveolar destruction and pulmonary edema. Although highly pathogenic viral and bacterial infections cause extensive accumulation of neutrophils in the lungs, how neutrophils mediate the progression of clinical manifestations leading to acute lung injury is not well understood. This project aims to explore the molecular mechanisms by which neutrophils contribute to ALI and ARDS in mouse models infected with influenza A H1N1 and H3N2 viruses, as well as in secondary pneumococcal pneumonia. The objectives include: (1) To evaluate the progressive changes in the lungs and contribution of neutrophils and their mediators in pulmonary complications of ALI/ARDS during primary and secondary pneumonia. (2) To explore opportunities for intervention by treatment with inhibitors against neutrophil recruitment (e.g. P38 MAPK inhibitor), neutrophil elastase and NADPH oxidase which will be tested in combination with antimicrobial agents – this will evaluate whether such interventions alleviate complications of pulmonary edema and alveolar injury. (3) To compare and characterize NETs formation in response to infection with different strains of *Streptococcus pneumoniae* of varying virulence, and whether antimicrobial combination therapy can ameliorate their deleterious effects. (4) To determine the contributions of pneumococcal virulence factors to NETs formation.