**University of Leicester**

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| **Project Reference** | BRC Studentships |

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**Section 2 – *Project Information***

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| **Project Title** | Development of an in vitro culture system to study the lung microcosm in airway diseases | |
| **Project Highlights:** | 1. | Characterise complex interactions of microbes and viruses within the lung microcosm. |
| 2. | Gain mechanistic insight about the role of the lung microbiome as a driver of chronic airway diseases and their exacerbations. |
| 3. | Identify microbiome-based interventions to improve health outcomes |
| **Project Summary** | | |
| **Background:** The lung is an ecosystem of microbial communities, including viruses, termed the microbiome [1, 2]. The members of these communities are metabolically and functionally active, and form ecological interactions within complex networks shaped by the structural and biological constrains of the respiratory system [3]. The ecology of the lung’s microbiome has been linked with chronic respiratory diseases including asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF) and interstitial lung diseases, therefore involving a wide range of pathophysiological mechanisms [4]. Even though high throughput sequencing approaches have a tremendous contribution in the discovery of microbiome shifts in disease, there is little understanding about what causes them as well as the extent of the intra- and inter-individual variability. This lack of mechanistic insight largely contributes to the slow transition from discovery to applicable microbiome-based interventions for improved health outcomes.  **Research Plan:** We will develop an in vitro model of the lung microbiome in asthma and COPD. This will be based on the Winogradsky culture system previously used in CF [5] with the aim to mimic the microenvironment of a mucus-filled bronchiole (e.g. pH, O2 and chemical profile). As proof-of-concept, we will inoculate the system with clinical airway specimens from patients with and without disease exacerbations. Using time-lapse analysis of metagenomic, meta-transcriptomic, and mass spectrometry data we will measure the taxonomic, functional and metabolic activity and biofilm formation [6, 7]. We will use mathematical modelling to: (1) describe cross-species ecological interactions and biotic shifts towards disease state-specific niches, and (2) dissect exacerbation dynamics with respect to clinical disease expression, physiology and inflammatory status.  **Data will be used to:** Develop an in vitro model of the airway microbiome, and to provide mechanistic insight on the dynamic interactions within the microbial communities and the lung microenvironment during respiratory disease exacerbations.  **Expected outcomes and impact:** The project aims to establish a model of the lung microcosm. Direct applications include the study of personalised microbiome disease-specific niches of the airways (including infections), the characterisation of the effect of environmental perturbations (therapy, antimicrobials, pollutants) on the microbiome, and the development of microbiome-based interventions including phage therapy. The system will provide invaluable support for the translational and basic research performed across the NIHR and the University of Leicester and specifically in the Centre for Phage Research, the Institute for Precision Medicine, the Respiratory Department, and the Leicester Microbial Sciences and Infectious Diseases Centre. | | |
| **References**  1. Man, W.H. et al. (2017) The microbiota of the respiratory tract: gatekeeper to respiratory health. Nat Rev Microbiol 15 (5), 259-270. 2. Choi, S. et al. (2021) Lung virome: New potential biomarkers for asthma severity and exacerbation. J Allergy Clin Immunol 148 (4), 1007-1015 e9. 3. Budden, K.F. et al. (2019) Functional effects of the microbiota in chronic respiratory disease. Lancet Respir Med 7 (10), 907-920. 4. Natalini, J.G. et al. (2022) The dynamic lung microbiome in health and disease. Nat Rev Microbiol, 1-14. 5. Quinn, R.A. et al. (2015) A Winogradsky-based culture system shows an association between microbial fermentation and cystic fibrosis exacerbation. ISME J 9 (4), 1024-38. 6. Quinn, R.A. et al. (2018) Niche partitioning of a pathogenic microbiome driven by chemical gradients. Sci Adv 4 (9), eaau1908. 7. Esteban, D.J. et al. (2015) Temporal and Spatial Distribution of the Microbial Community of Winogradsky Columns. PLoS One 10 (8), e0134588. | | |