Project Details	
Project Code	MRC21IIRBr Weavers
Title	Integrating novel animal models and human genetic epidemiology to explore chronic inflammatory lung disease in vivo and test innovative anti-microbial strategies
Research Theme	Infection, Immunity & Repair
Summary	Chronic inflammatory lung conditions involve self-perpetuating cycles of airway damage, inflammation and infection and affect 400 million people worldwide. Innovative treatments are urgently required, particularly with rising antimicrobial resistance. Using state-of-the-art microscopy and transcriptomics in Drosophila, together with genetic epidemiology, we will explore disease progression in vivo, test novel therapeutic strategies and study links to human disease.
Description	Chronic inflammatory lung conditions are among the most frequent non-communicable diseases worldwide, affecting over 12 million people in the UK alone. Some of these conditions, such as chronic obstructive pulmonary disease (COPD), are triggered by exposure to environmental stimuli (e.g. pollutants or tobacco smoke). Others are genetic disorders, such as cystic fibrosis (CF) caused by dysfunction of the epithelial anion channel cystic fibrosis transmembrane conductance regulator (CFTR). Strikingly, these disorders share common pathological features and are characterised by self-perpetuating cycles of lung damage, mucus production, infection and inflammation. The persistent inflammatory response is more harmful than protective and a major driver of disease progression, causing dramatic destruction of healthy lung tissue that eventually results in respiratory failure and death (1). Despite considerable efforts to find new therapies, these debilitating conditions remain difficult to treat. Current treatments that target inflammation are non-specific and unsuitable for long-term use because of their adverse effects. There is also a disturbing increase in the incidence of antimicrobial resistance. New treatments must be developed that reduce inflammation without compromising anti-microbial defences. There is a clear need for more experimentally-tractable, non-vertebrate models to investigate airway disease in vivo. We have already established the fruitfly Drosophila as an invaluable model to dissect fundamental mechanisms driving inflammation and tissue repair (2,3). Since Drosophila express homologues of CFTR and develop CF- and COPD-like pathologies (4,5), they represent an exciting invertebrate model to accelerate our understanding of chronic inflammatory lung disease. In this PhD, we will integrate in vivo studies in Drosophila with human genetic epidemiology to dissect the cellular and molecular mechanisms driving these inflammatory conditions. Using state-of-the-art microscopy we will explore disease progression in vivo and live-image the dynamic interactions between key cell types in the airway microenvironment. We will employ cutting-edge transcriptomic analysis on isolated cells to identify gene expression signatures associated with these conditions; this will be followed by tissue-specific genetic manipulation in Drosophila, together with human genetic epidemiology approaches, to functionally characterise novel genes and explore their links to human disease. Finally, we will use our in vivo models as pre-clinical platforms to test innovative therapeutic drugs, including novel

	antimicrobials. This PhD brings together a multi-disciplinary team of researchers from Bristol and Cardiff with expertise in tissue repair, inflammation, microbiology and respiratory disease. The work has wide-ranging clinical relevance as our findings will be highly relevant to other chronic inflammatory diseases, such as asthma, cardiovascular disease and neurodegenerative conditions. The student will learn skills in in vivo biology, state-of-the-art live imaging, genetic manipulation, transgenic line creation (e.g. CRISPR), microbiology, bioinformatics, molecular biology and human genetic epidemiology. In addition, the candidate will have the opportunity to utilise cutting-edge technologies, including flow cytometry and transcriptomics. References: 1.Barnes et al (2015) Nature Review Disease Primers 1:15076 2. Weavers et al (2019) Current Biology 29(22):3851-3862 3. Weavers et al (2016) Cell 165(7):1658-1671 4. Kim et al.(2020) PNAS 117(19):10357-10367 5. Prange et al (2020) Ageing 10(8):2122-2135
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