Project Details	
Project Code	MRC21IIREx Scotton
Title	COVID-19 and lung disease: developing therapy through immune cell re-programming
Research Theme	Infection, Immunity & Repair
Summary	Our expert team of respiratory scientists/clinicians will support and nurture you to become an independent researcher with a broad range of lab skills. We need your help to test novel drugs to re-program the immune system to reduce progression of deadly lung diseases (including COVID-19, which needs no introduction!). You will work with clinical samples, in vitro/vivo models including the use of induced pluripotent stem cells, bioinformatics and advanced imaging.
Description	SARS-CoV-2 infection of the respiratory tract can lead to mild or severe disease (COVID-19). Ageing is a crucial risk factor, alongside male sex and co-morbidities such as hypertension and diabetes. The same risks are key in other serious, incurable and fatal lung diseases such as pulmonary fibrosis (PF) and chronic obstructive pulmonary disease (COPD). Emerging data suggest that COVID-19 can lead to lung scarring (i.e. PF), and patients who have PF have greater mortality from COVID-19. PF already accounts for 1% of all UK deaths, while COPD is the 3rd biggest killer globally. Our recent analysis using the UK Biobank (a resource of genetic, biomarker and health data for over 500,000 participants) has revealed intriguing associations with immune cell numbers and also telomere attrition in PF and COPD (accepted for publication in the Lancet Respiratory Medicine); we are following up some of these findings in our joint Exeter-Bristol patient cohorts. Immune cell repertoires are also a major research focus in COVID-19. Macrophages (MΦ) play a key role in defence in against pathogens, but can also contribute to disease development - not least via the overproduction of inflammatory cytokines (seen in both PF and COVID-19) - and this is linked to mitochondrial function. Mitochondria are key regulators of cellular activity, act as intracellular signalling 'hubs' for viral infection, and mediate the cellular response to inflammation through the inflammasome; they are also targets for SARS-CoV proteins. Effective immunity deteriorates with age, leading to immunosenescence and chronic low-grade inflammation. Our two recent MRC awards (totalling >£1.5m) focus on mitochondria in the context of COPD and PF. We have exciting data showing that novel drugs developed by Prof Whiteman, which generate physiological doses of mitochondrial-targeted hydrogen sulfide (H2S), can ameliorate pro-inflammatory and pro-fibrotic responses in experimental systems. MΦ mitochondria are a novel drug target to control innate immune activity. Recent work from Prof Lindsay has further focused on the role of long non-coding RNA (lncRNA) in the regulation of inflammatory responses in MΦ, while preliminary data from Dr Scotton's group has demonstrated that adoptive transfer of human MΦ can exacerbate fibrotic disease in murine models. Our hypothesis is that "mitochondrial dysfunction in MΦ can be modified by our novel H2S drugs to alter cellular metabolism and transcriptome, reducing hyper-activation and facilitating tissue repair". These processes will be relevant for disrupted MΦ function in both PF and COVID-19. There are 3 Aims: 1) Characterise the lncRNA/mRNA transcriptome and

	phenotype of monocyte-derived macrophages from patients with PF versus age-matched (~60 year old) and young controls using RNA-Seq, bioinformatics, and standard in vitro assays (e.g. cytokine ELISA, flow cytometry, chemotaxis, and phagocytosis) during the response to: a) inflammatory stimuli, including heat-inactivated SARS-CoV-2 viral particles and Spike protein, and b) macrophage polarisation e.g. M(LPS), M(IL4). 2) Interrogate the functional consequence of H2S drug supplementation on macrophage function and lncRNA levels in human MΦ, ± stimulation with LPS, IL-4 or SARS-CoV-2/Spike protein. Induced pluripotent stem cell-derived alveolar MΦ will also be used to increase relevance to the lung. 3) Determine the fibrogenic potential of young-vs-old human MΦ following adoptive transfer into immunocompromised NOD/SCID mice in an experimental in vivo model of PF, and the therapeutic benefit of our H2S drugs. Ultimately, we would like to translate these novel drugs from bench to bedside. Methodology: RNA-Seq; qRT-PCR; ELISA; flow cytometry of MΦ phenotype/function; Seahorse extracellular flux analysis; experimental mouse model of PF; In Vivo Imaging System (IVIS) tracking of fluorescently-tagged MΦ; measurement of lung collagen accumulation and ex vivo micro-Computed Tomography
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