Project Details	
Project Code	MRCPHS24Ex Scotton
Title	Genetic predisposition to accelerated ageing: targeting telomeres using sex hormone supplementation in Idiopathic Pulmonary Fibrosis
Research Theme	Population Health Sciences
Summary	Lung fibrosis is a devastating disease which causes 1% of UK deaths. On average, patients only survive 2-3 years after diagnosis. Ageing is a big risk factor; patients often have unusually short telomeres, correlating with a reduction in sex hormone levels. We will investigate if boosting hormone levels might improve telomere length and reduce disease burden - using data from cutting-edge lab experiments with lung cells, combined with analyses of patient genetics.
Description	Idiopathic pulmonary fibrosis (IPF) is a hugely debilitating disease of ageing, which has a dismal prognosis and a 5-year survival of only 20%. IPF accounts for around 5300 deaths each year (1% of all UK deaths). Current anti-fibrotic medications are expensive (£27k per patient per annum) and only slow disease progression, while having limited benefit for quality of life (largely due to a range of unpleasant side effects). New therapies are therefore paramount. This proposal represents a novel opportunity to help establish the mechanism and potential efficacy of using sex hormone supplementation as a treatment. The project will employ a powerful combinatorial approach of genetic analyses, access to patient samples and cutting-edge in vitro approaches to ascertain how sex hormones may be able to boost telomere length and thereby revert one of the key hallmarks of ageing which may underpin disease development. This is a hugely exciting training opportunity in a wide range of cell and molecular biological techniques and bioinformatics. It has conceptual buy-in from our dedicated patient and public involvement group (PPIEG), and ongoing liaison with our PPIEG will also be an important part of the project. Work from Dr Anna Duckworth, published in Lancet Respiratory Medicine, provided evidence of a causal role for prematurely-shortened telomeres in IPF using genetic analyses of data from UK Biobank (PMID: 33197388). This indicates an accelerated ageing process – partly explaining the cellular senescence seen in fibroblasts/epithelial cells in IPF lungs. Telomere biology disorders (such as dyskeratosis congenita) are treatable using androgens (sex hormones). Sex-related differences in organ fibrosis indicates a role for sex hormones in progression. One potential mechanism of action is via oestrogen acting on the promoter region of the TERT gene; TERT encodes telomerase - the rate-limiting enzyme in telomere maintenance. Through collaboration with Prof Murray, our current work in UK Biobank has revealed strong evidence of a protective effect for sex hormones in males and females with IPF. The precise mechanism is unknown. Similarly, we do not know the impact of single nucleotide polymorphisms in telomere-related genes (associated with IPF from genome-wide association studies) on the TERT response to oestrogen. Our ongoing clinical study is measuring sex hormone levels and telomere length in 100 IPF patients recruited via the Royal Devon & Exeter hospital. This proposal is multi-factorial, combining bioinformatics analysis, patient samples and in vitro cell biology to investigate whether sex hormone supplementation can boost telomere length in disease-

	relevant cell types: Aim 1) Leveraging UK Biobank data (whole exome/genome sequencing, leukocyte telomere length), perform targeted analysis of genetic variants in telomere-related genes (TERT/TERC/RTEL1/PARN) and their impact. Aim 2) Using existing (and ongoing) biobanked patient samples, investigate how sex hormone supplementation (oestrogen/testosterone) in complex in vitro models of IPF impacts pro-fibrotic cell biological responses and telomere-maintenance pathways. This will include co-culture of epithelium/fibroblasts/macrophages and precision cut tissue slices. Aim 3) Combine data from Aims 1/2 to recapitulate findings using cell types with defined genetic variants in telomere-maintenance genes (generated from genotyped-patients or introduced into existing cells using gene targeting approaches). These data will help define the mechanism by which sex hormone supplementation affects telomere maintenance, taking into account the genetic landscape of the individual. Combined with our ongoing observational clinical study, this will provide the mechanistic evidence base for a prospective assessment of sex hormone therapy in patients with IPF.
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