Project Details	
Project Code	MRCIIAR25Ex Scotton
Title	Genetic predisposition to accelerated ageing: targeting telomeres using sex hormone supplementation in chronic lung disease
Research Theme	Infection, Immunity, Antimicrobial Resistance & Repair
Summary	Lung fibrosis is a devastating disease which causes 1% of all UK deaths. On average, patients only survive 2-3 years after diagnosis. Ageing is a big risk factor; patients often have unusually short telomeres (the protective shields at the ends of our chromosomes). This shortening appears to be linked with reduced sex hormone levels in the blood. 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), although this is likely to be an underestimate. 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. It is therefore paramount to identify new therapies which are more effective and better tolerated by patients. 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. A key hallmark of ageing is the progressive shortening of the telomeres which protect the ends of our chromosomes from becoming damaged. However, the mechanisms are poorly understood by which sex hormones may be able to boost telomere length and thereby reduce the detrimental impact of ageing which underpins disease development. This is a hugely exciting training opportunity in a wide range of cell and molecular biological techniques, genetics 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. The student would therefore meet with patients, benefit from their insights, and hence co-develop various aspects of the study with a view to delivering the most clinically-meaningful results. Co-supervisor Dr Anna Duckworth recently graduated from the GW4 MRC DTP herself, and has now taken on the role of "Patient Engagement And Research Lead" as a bridge between the University of Exeter and the Royal Devon University Hospital. Her PhD work, published in the 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 sometimes treatable using androgens (sex hormones). Sex-related differences in organ fibrosis also indicate a role for sex hormones in progression - and 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, 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 recently completely clinical study, led by Dr Duckworth, measured sex hormone levels and telomere length in 102 IPF patients (plus age- and sex-matched controls) recruited via the Royal Devon University Hospital. This study has provided further evidence supporting this fascinating link. This proposal is therefore 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. The main aims are: 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 observational clinical study, this will provide the mechanistic evidence base running alongside the development of an NIHR EME bid for a prospective assessment of sex hormone therapy in patients with IPF - this is a really exciting prospect.
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