Project Proposal Form

**Section 1 – *Supervisor Information***

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| **First Supervisor (Name and Title)** | Dr Katy Roach (Lecturer in Respiratory and Precision Medicine) |

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| **Proposed Second Supervisor** | Prof. Louise Wain (GSK/British Lung Foundation Chair in Respiratory Research) |
| **Additional Supervisor** |  Dr Richard Allen |

**Section 2 – *Project Information***

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| **Project Title** | Functional investigation of a potential novel drug target for progressive lung fibrosis |
| **Project Highlights:** | 1. | Investigation of a potential new drug target for a currently incurable lung disease |
| 2. | Interdisciplinary project providing training and expertise in bioinformatics, statistical genetics, cellular and molecular biology |
| 3. | Supervisory team comprising Leicester’s ‘rising star’ ECRs (Roach and Allen) with complementary expertise in genomic epidemiology and human lung models of fibrosis |
| **Project Overview**  |
| Idiopathic pulmonary fibrosis (IPF) is an irreversible progressive disease characterised by excessive scarring of the lung due to unknown causes. IPF has a median survival of 3-5 years and the drugs licensed for treating IPF only slow progression of disease and are not effective in all patients.Genome-wide association studies (GWAS) test genetic variants from across the genome for their association with disease; associated variants are then mapped to likely causal genes and thereby generate new testable hypotheses about disease mechanisms. Drug targets with support from genetic studies have been shown to be significantly more likely to be successful in clinical development[1] and therefore the use of GWAS data in prioritisation of new potential targets for further investigation has been widely adopted. Published GWAS of IPF risk (i.e. comparing IPF cases and controls), have implicated genes involved in host defence, cell-cell adhesion, TGFβ signalling, telomere maintenance and spindle assembly as important processes in disease pathogenesis[2-4]. IPF is a heterogeneous disease; identification of genes that drive more progressive disease sub-types may indicate more effective targets for precision medicine intervention in established disease. We have recently undertaken the first GWAS of lung function decline in a large IPF case population and identified a robust genome-wide significant signal which implicates an interesting new gene. The gene encodes a serine/threonine protein kinase which is expressed in fibroblasts and has been implicated in fibrotic processes underlying atrial fibrillation **but has not previously been explored in relation to IPF**. Furthermore, aninhibitor of the encoded kinase is in the early stages of development. This interdisciplinary project will integrate bioinformatics, genetic epidemiology and cellular- and molecular biology to define the role of the gene and it’s productin lung fibrosis and it’s potential as a new drug target for IPF.**Project aims:** **1)** Bioinformatic validation of the causal gene driving the association signal *(year 1).***2)** Investigate gene expression in human lung myofibroblasts (HLMFs) and human IPF lung tissue *(year 2).***3)** Define the role of the encoded kinasein HLMF pro-fibrotic function using primary cells and established human lung models of fibrogenesis[5, 6] *(year 3).* |
| **Methodology**  |
| **Aim 1** Fine-mapping of the locus will be undertaken using new IPF array-genotyped and whole genome and exome sequenced (WES/WGS) datasets. Integration of genetic data with publicly available bulk and single-cell gene and protein expression datasets, epigenomic maps and Hi-C data will be used to define the allelic series of gene expression and IPF associated variants at the chromosome 1 locus to inform experiments in Aim 2/3. The student will develop skills in statistics, R programming, high performance computing and interrogation of large-scale bioinformatics resources. **Aim 2** Gene expression will be examined in non-fibrotic and IPF derived HLMFs both at rest and following TGFβ1 stimulation, and in IPF subject lung resection specimens. The student will gain experience in qRT-PCR, western blot and immunohistochemistry techniques. **Aim 3**Using siRNA knockdown or novel inhibitors, the role of the kinase in HLMF pro-fibrotic functions, such as proliferation, contraction and collagen secretion will be investigated.  |
| **References** | Roach KM et al (2021) Evaluation of Pirfenidone and Nintedanib in a Human Lung Model of Fibrogenesis Front Pharmacol 12:679388. doi: 10.3389/fphar.2021.679388. eCollection 2021.Virk HS... Roach KM (2021) TGFβ1 induces resistance of human lung myofibroblasts to cell death via down-regulation of TRPA1 channels. Br J Pharmacol 178(15):2948-2962. doi: 10.1111/bph.15467. Roach KM et al (2018) A model of human lung fibrogenesis for the assessment of anti-fibrotic strategies in idiopathic pulmonary fibrosis. Sci Rep 8(1):342. doi: 10.1038/s41598-017-18555-9.Allen RJ.... Wain LV (2021) Genome-wide association study across five cohorts identifies five novel loci associated with idiopathic pulmonary fibrosis. medRxiv doi: https://doi.org/10.1101/2021.12.06.21266509Leavy OC....Wain, LV, Allen RJ (2021) Proportion of Idiopathic Pulmonary Fibrosis Risk Explained by Known Common Genetic Loci in European Populations. Am J Respir Crit Care Med 203(6):775-778. doi: 10.1164/rccm.202008-3211LE.Allen RJ.... Wain LV (2020) Genome-Wide Association Study of Susceptibility to Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med 201(5):564-574. doi: 10.1164/rccm.201905-1017OC. |

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2. Allen, R.J., et al., *Genetic overlap between idiopathic pulmonary fibrosis and COVID−19.* medRxiv, 2021: p. 2021.12.08.21267459.

3. Allen, R.J., et al., *Genome-Wide Association Study of Susceptibility to Idiopathic Pulmonary Fibrosis.* American journal of respiratory and critical care medicine, 2020. **201**(5): p. 564-574.

4. Dhindsa, R.S., et al., *Identification of a missense variant in SPDL1 associated with idiopathic pulmonary fibrosis.* Communications biology, 2021. **4**(1): p. 392-392.

5. Roach, K., et al., *Evaluation of Pirfenidone and Nintedanib in a Human Lung Model of Fibrogenesis.* Frontiers in Pharmacology, 2021. **12**(2805).

6. Roach, K.M., et al., *A model of human lung fibrogenesis for the assessment of anti-fibrotic strategies in idiopathic pulmonary fibrosis.* Scientific Reports, 2018. **8**: p. 15.