**University of Leicester**

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| **Project Reference** | BRC Studentships |

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| **First Supervisor** | ​Dr Katy Roach |
| **School/Department** | ​Respiratory Sciences​ |
| **Email**  | ​kmr11@le.ac.uk  |

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| **Second Supervisor** | ​Prof. Peter Bradding ​ |
| **School/Department** | ​University of Leicester​ |
| **Email**  | ​pb46@le.ac.uk  |

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| **Additional Supervisor** | ​Dr Harvinder Virk​ |

**Section 2 – *Project Information***

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| **Project Title** | ​  |
| **Project Highlights:** | 1. | TRP channels in human lung fibrosis  |
| 2. | Ion channels as therapeutic targets |
| 3. | Treatments for IPF |
| **Project Summary**  |
| Idiopathic pulmonary fibrosis (IPF) is a progressive disease of unknown aetiology that leads to respiratory failure and death. Fifty percent of patients with IPF die within 3 years of diagnosis, an outcome worse than many cancers. Its incidence continues to rise by 10% annually with >5000 incident cases per year currently in the UK. There are only two licensed treatments for IPF, pirfenidone and nintedanib. Novel, more effective and better tolerated treatments are therefore required urgently to address this unmet clinical need. TGFβ1-mediated myofibroblast activation contributes to pathological fibrosis in many diseases including idiopathic pulmonary fibrosis (IPF). Ca2+ signalling is necessary for diverse cellular activities including myofibroblast activation and pro-fibrotic functions. Dr Roach’s group have identified various ion channels as potential therapeutics for IPF. Transient Receptor Potential (TRP) channels, in particular, have recently been shown as the major Ca2+-permeable channel in human atrial fibroblasts, driving pro-fibrotic functions.In this study we aim to examine TRP-mediated Ca2+ signals for their effect on myofibroblast proliferation and differentiation from IPF patients.Using our pool of myofibroblasts and paraffin embedded tissue from non-fibrotic and IPF donors we will examine the mRNA, protein and tissue expression of specific TRP channels at basal and following stimulation with TGFβ1 and TGFβ3. Using techniques such as patch clamp electrophysiology, cellular culture, RT-PCR, western blot assays, MTS assays and flow cytometry we will examine the functional role of specific TRP channels in human lung myofibroblast. In addition, we have established an ex-vivo human lung parenchymal model of TGFβ1-dependent fibrogenesis. We aim to use the model to study TRP channels but also to develop this model further by optimising lentiviral overexpression and knockdown constructs in human ex-vivo lung tissue. |
| **References**1. Virk HS, Biddle MS, Smallwood DT, Weston CA Castells E, Feghali-Bostwick C, Bowman VW, McCarthy J, Amrani Y, Duffy SM, Bradding P, **Roach KM**. TGFβ1 induces resistance of human lung myofibroblasts to cell death via downregulation of TRPA1. *Br J Pharmacol*, *2021 Mar, doi: 10.1111/bph.15467.*
2. **Roach KM**, Castells E, Dixon K, Mason S, Elliott G, Marshall H, Poblocka MA, Macip S, Richardson M, Khalfaoui L, Bradding P. Evaluation of pirfenidone and nintedanib in a human model of lung fibrosis. *Frontiers in Pharmacology* 2021. 12(2805).
3. **Roach KM.,** Sutcliffe A., Matthews L., Elliott G., Newby C., Amrani Y, Bradding P. "A model of human lung fibrogenesis for the assessment of anti-fibrotic strategies in idiopathic pulmonary fibrosis." Sci Rep 2018; 8: 15.
4. **Roach KM**, Bradding P. Ca 2+ signalling in fibroblasts and the therapeutic potential of K Ca 3.1 channel blockers in fibrotic diseases. *Br J Pharmacol*, *2020 Mar;177(5):1003-1024.*
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