CRUK Cambridge Centre Clinical PhD project

PhD Project Title	Understanding the molecular basis of increased cancer risk in familial pulmonary fibrosis
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Laboratory Location	CIMR

Project Outline	Cancer and fibrotic diseases share many pathogenic pathways [1]. Studying these commonalities may help find treatments for both conditions. Pulmonary fibrosis is a chronic fibrosing disease associated with an increased incidence of lung cancer [2]. The cause of cancer in pulmonary fibrosis is not well understood, at least in part because the initiating mechanisms of pulmonary fibrosis remain mysterious [3]. Importantly the association of pulmonary fibrosis and cancer is recapitulated in individuals with monogenic inherited forms of pulmonary fibrosis, which made offer a unique window into the early pathologies [4]. **We hypothesise that understanding genetic forms of pulmonary fibrosis will identify novel pathogenic mechanisms relevant both to fibrosis and to lung cancer**. We aim to elucidate the cellular dysfunction resulting from expression of the most common pathogenic mutant of surfactant protein C (SFTPC-I73T) and thereby understand the early events of pulmonary fibrosis that create an environment where malignant transformation can occur.
Experimental plan	**Key question 1: How is SFTPC-I73T mistrafficked in cells?** Preliminary data show that SFTPC is mistrafficked to the cell surface rather than multivesicular bodies. This mistrafficking is associated with impaired SFTPC monoubiquitination. By manipulating the ubiquitination and ESCRT machineries we will determine if impaired monoubiquitination is the cause or a consequence of mistrafficking. **Key question 2. What are the effects of altering SFTPC's interactome?** Preliminary data show that SFTPC-I73T loses the ability to bind to the integrin MPZL1 causing MPZL1 mistrafficking. We will determine the consequences of altered MPZL1 trafficking on cell mobility, proliferation and apoptosis. **Key question 3. Are these changes replicated in type II pneumocytes?** The poor quality of alveolar type II cell (AECII) models has limited surfactant biology research. With Pieter Hiemstra (University of Leiden) we have generated iPSC-derived AECIIs. With Dr Joo-Hyeon Lee (Stem Cell Institute, Cambridge) we have generated lung organoids from AECIIs. The discoveries made in cell lines (Key questions 1 and 2) will be validated in these physiological models to ensure relevance in pulmonary biology.
Main Techniques	• Cell line culture, proteomics, flow cytometry, advanced microscopy. • E*x vivo* models of type 2 pneumocytes (iPSC-derived and 3D organoids)
Key References	1. Common pathways in idiopathic pulmonary fibrosis and cancer. Eur Respir Rev. 2013 Sep 1;22:265-72. 2. Lung cancer and cryptogenic fibrosing alveolitis. A population-based cohort study. Hubbard R *et al* Am J Respir Crit Care Med 2000;161:5-8 3. Lung cancer in patients with idiopathic pulmonary fibrosis. Karampitsakos T *et al*. Pul Pharmacol Ther 2017;45:1-10

	4. Genetic defects in surfactant protein A2 are associated with pulmonary fibrosis and lung cancer. Wang Y *et* al. Am J Hum Genet 2009;84:52-9