CRUK Cambridge Centre Clinical PhD project

PhD Project Title	**Mechanisms underpinning the link between COPD/emphysema and lung cancer**
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Programme	Aerodigestive Cancers
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Laboratory Location	Department of Biochemistry; Department of Medicine

Project Outline	**Aims and objectives** Lung cancer is the most common cause of cancer-related mortality. The reasons that outcomes are so poor are that patients with lung cancer present late, at a stage when the disease is incurable; and secondly that currently available treatments for the majority of patients are ineffective. Further, there are currently no therapeutic interventions that are licensed for chemoprevention. Early detection, early intervention and chemoprevention could transform outcomes in this devastating disease. There is therefore a clinical imperative to identify individuals at high risk of lung cancer, understand why they are at risk and implement novel strategies to prevent and treat the disease. There is an excess risk of lung cancer in patients with COPD/emphysema (after correction for smoking history). NRF2 is a master antioxidant transcription factor with complex links to both COPD and lung cancer. Preclinical data suggests that elevated NRF2 activity is protective in COPD and further that an effective NRF2 antioxidant response is protective in terms of developing lung cancer, but that it is subverted, overactive and protumorigenic in established malignancy. NRF2 is primarily regulated by KEAP1, a substrate adaptor for an E3 ubiquitin ligase. Drugs are under development to target this pathway for chemoprevention. A key question is who may benefit given the potential janus-like impact of NRF2 agonists. This will be the first project to address this issue in patient-derived specimens.
Experimental plan	Patients with well phenotyped COPD with and without lung cancer will be recruited. Biopsies from distal airways+/-cancer tissue will be genotyped for KEAP1/NRF2 pathway mutations using targeted NGS and phenotype (histology/IHC to assess NRF2 pathway status). Primary bronchial epithelial cells (PBECs) will be expanded using a recently published protocol already established in the laboratory. Functional studies (propensity to form dysplastic lesions, impact of NRF2 agonists, CRISPR/lenti manipulation of pathway etc) will be performed using PBECs in an established organotypic air-liquid interface culture system. Collaboration with the Cambridge Cancer Centre Early Detection theme on this cohort will be sought and appropriate samples banked for biomarker analyses. This project will establish a unique pipeline for the investigation of patients with COPD/lung cancer patients in Cambridge. It will inform genotype-phenotype associations, provide a functional readout of NRF2 agonist activity in that context and build a platform for true multidimensional analyses of these patients to inform pathogenesis and the potential for chemoprevention.

Main Techniques	The clinical fellow will be highly motivated and interested in a high quality translational project that offers comprehensive training in key laboratory techniques: **1**. **Clinical**: • patient recruitment • primary cell harvest at bronchoscopy (with clinical team/senior consultant colleague support/collaboration) **2. Cell biology**: • expansion and propagation of primary human respiratory epithelial cells • complex primary 3D tissue culture • advanced histological and microscopic techniques **3**.**Molecular biology**: • targeted next generation sequencing of human specimens • lentiviral and CRISPR based manipulation of specific gene targets **4. Screening response to lead compounds with potential for chemoprevention/ interaction with KEAP1/NRF2**
Key References	1. **Correia LL,…, McCaughan FM**. *Bronchial Dysplasia in a Novel Organotypic Model of Early Human Squamous Lung Cancer. doi: 10.1164/rccm.201510-2084OC. Am J Respir Crit Care Med. 2017 SOX2 Drives* ***2.*** **M. C. Jaramillo, D. D. Zhang**, *The emerging role of the Nrf2-Keap1 signaling pathway in cancer. Genes Dev 27, 2179-2191 (2013).* ***3.*** **D. A. Abed, M. Goldstein, H. Albanyan, H. Jin, L. Hu***, Discovery of direct inhibitors of Keap1-Nrf2 protein-protein interaction as potential therapeutic and preventive agents. Acta Pharm Sin B 5, 285-299 (2015).*