Clinical PhD Project 2024

Towards a strategy for the early detection of lung cancer in never-smokers (LCINS)

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Principal supervisor's CRUK CC theme: Thoracic Cancer Programme

Department for student registration: Medicine
Department or institute where research will take place: Heart and Lung Research Institute

Postgraduate scheme: **Clinical Research Training Fellow (3-year PhD)**

PhD project outline:

In the UK, Lung Cancer in Never-Smokers is responsible for an estimated 6000 deaths per year making it the 8th most common cancer in the UK if considered as a distinct disease entity. The global prevalence of LCINS is increasing and there is evidence that risk factors vary depending on the population and geographical region studied. The demographics of those populations affected by LCINS include a female predominance and potentially under-represented groups (ethnicity, social deprivation). There is little known about the specific risk factors in the UK and with colleagues supported by the National Cancer Research Institute, we have recently described a road map to addressing this in the UK (see reference 1). In this review, we acknowledge this is a challenging area but the epidemiology and impact of this disease mandate a novel approach.

Aims
1) Establish a regional registry of patients with LCINS and invite them to enrol in a) a retrospective analysis or b) a prospective longitudinal study as appropriate
2) Establish a personalised environmental exposure record on the basis of structured in-depth interviews and available exposure data from public records
3) Multiparametric profiling of tumour specimens and paired blood samples to interrogate mutational burden, signatures and potential measures of risk
4) Integration of the molecular analysis, environmental profiling and personal exposure to determine whether it is possible to define a UK risk-profile for LCINS

PhD experimental plan:

This is translational project suitable for a clinician interested in applied clinical research.

Participants will be invited to join via existing patient cohorts in NHS clinics for the retrospective analysis. Patients who meet the following criteria – never-smokers, archived biopsy samples available, consent to access archived samples and to provide blood for germline DNA and paired plasma analysis - will be recruited to establish a cohort of patients. Some individuals with pre-treatment samples have already been banked.

A prospective cohort with the potential to include longitudinal blood and/or tissue sampling will also be recruited.

A parallel study on indeterminate lung nodules in lung cancer (Reference 2 – MISIL1 study) will report in the next months before this fellowship begins. It will integrate multiple different proposed biomarkers – circulating DNA (whole genome), methylated DNA, proteomics, cytokines and circulating autoantibodies – to attempt to distinguish benign and malignant nodules.

If a multiparametric biomarker is successfully generated in MISIL1, it will be assessed in these cohorts to determine whether it may be a valid approach to early diagnosis of LCINS. In any event similar protocols will be applied to the samples from this cohort.

The genomic analysis will include signatures that may relate to environmental exposure and this information will be integrated with the reported environmental exposure.

The Sherlock Study is applying a similar approach in a non-UK population. Given differences in demographics and environmental exposures, it is critical that a UK population and risk is assessed.

Main techniques:

The project offers training in the design, management and delivery of clinical/translational trials suitable for a future academic clinical triallist. This will include direct patient contact, mixed methodology research including interview-based assessment as well as the molecular biology methods outlined above.

It will provide training in the application of cutting edge multiparametric molecular profiling of human tumour specimens and paired blood samples. This will include genomics and proteomic analysis.

The candidate will be expected to undertake training in bioinformatics and data integration/analysis.

Key references:

1. Khan, S., Hatton, N., Tough, D. et al. Lung cancer in never smokers (LCINS): development of a UK national research strategy. BJC Rep 1, 1 (2023). https://doi.org/10.1038/s44276-023-00006-w
2. https://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/multiparametric-stratification-of-indeterminate-lung-nodules-misil1/
3. https://dceg.cancer.gov/research/cancer-types/lung/sherlock-lung-study