PROJECT TITLE: Type-2 airway inflammation as a driver of progressive respiratory morbidity: A Predict and Prevent Approach in Obstructive Airways Disease

Supervisors: Professor Ian Pavord [Nuffield Department of Medicine (NDM)], Dr Nayia Petousi (NDM), Dr Helen Ashdown [Nuffield Department of Primary Care and Health Sciences (NDPCHS)]
[GSK supervisor not agreed, GSK main contact with: William Fahy, Respiratory Theme]

Overview: The obstructive airways diseases (asthma & COPD) affect >500,000 people worldwide and cause significant morbidity and mortality. Despite increased healthcare expenditure, patient outcomes remain poor. We suggest this is because diagnosis happens typically late in the disease process when irreversible damage to the airways and patient has occurred. Indeed, diagnosis and assessment rely on spirometry (conventional lung function tool) which lacks sensitivity to early small-airways inflammatory changes (where disease starts) and only detects already-established damage. The overarching aim of the research is to move away from this "fire-fighting approach" towards a "predict and prevent" approach where disease activity is identified *upstream* and treated before irreversible damage has occurred. Two key advances, developed in Oxford over the last decade, have opened the way for this: (1) recognition that type-2 eosinophilic airway inflammation is the most treatment-responsive disease-activity trait in airways diseases (steroids, monoclonal type-2 targeting antibodies), and importantly can be identified by easily-accessible biomarkers: exhaled NO (FeNO) and blood eosinophil count (BEC); (2) The development of an award-winning (RSC Horizon Prize 2022) highly sensitive non-invasive physiological technique for measuring disease activity within the lung [Computed Cardiopulmonography (CCP)] which offers the prospect of identifying early small-airway disease well before overt disease becomes apparent. There is also increasing evidence from large population cohorts that type-2 biomarkers are associated with lung function decline, evident both in airways cohorts (COPD, asthma) and in healthy populations.

Therapeutic Area, Disease Scope & Relevant Scientific Theme alignment: Respiratory Medicine, COPD, "Predictors of exacerbators and fast disease progression"

Project Description/Aims: As such, this research project aims to test the fundamental hypothesis: Is *subclinical* type-2 airway inflammation a driver of progressive airway pathology and consequently of clinical airways disease morbidity? If so, is this a reversible process? It will focus on two elements:
(1) Epidemiology – Large healthcare dataset: This component will utilise large healthcare databases, e.g. Clinical Practice Research Datalink (CPRD), a large database of routinely collected longitudinal primary care data with hospital episode linkage, to undertake a matched retrospective case-control study to answer the questions: (i) Is there an association between BEC earlier on in life with the development of clinical disease in later adulthood (i.e. obtaining a diagnosis of airways disease: asthma or COPD); (ii) Identify other epidemiological factors, clinical characteristics or risks, that influence the predictive power of BEC (and other markers) in the development of airways disease and disease progression (and exacerbations); (iii) describe the chronological trend, including stability or lack thereof, over time of BEC over the years prior to diagnosis.
(2) Lung physiology and airway biology: This component will combine the novel CCP technique with detailed clinical and biological phenotyping in relation to type-2 inflammation in blood (e.g. cytokines), breath (e.g. exhaled NO, VOCs), nasal sampling and sputum (eosinophil count, cytokines, transcriptomics), to address the questions: (i) Do apparently healthy individuals – no diagnosis of respiratory disease – but who have high biomarkers (FeNO $\geq$ 50 ppb and/or BEC $\geq$ 0.3 x10^9 cells/L) have evidence of type-2 eosinophilic inflammation in their airways (through immunobiology techniques examining induced sputum/nasal scrapes) associated with small-airway dysfunction (through the sensitive physiology index sigmaCL from CCP). Type-2 high individuals will be studied and compared with type-2 low (FeNO <25 ppb, BEC <0.15 x10^9 cells/L) participants. (ii) Are subclinical physiological airway changes identified in type-2 high individuals reversible through treatment that targets Type-2 inflammation (proof-of concept experimental medicine study). (iv) Describe relationships between Type-2 markers/symptoms/small-airway dysfunction in an at-risk cohort (with no established airways disease diagnosis) to better understand progressive airway pathology (e.g. progression to COPD).

Impact: The project will set the groundwork for future studies on clinical disease risk (e.g. longitudinal prospective cohort establishment to define target populations for screening/primary prevention) and clinical trials targeting

Type-2 traits earlier in a patient's journey to investigate if early therapeutic intervention may be of benefit in preventing disease progression or development of airways disease later on in life.

Training for Student and Research Environment: The student will have the opportunity to train in an inter-disciplinary research environment that spans clinical respiratory medicine, human physiology/molecular biology and epidemiology, with a focus on data science. In particular, in addition to training through the OBDS programme, training opportunities include gaining experience and expertise in:

- Integrative respiratory physiology, and in particular using a state-of-the-art technology to measure lung function (CCP), which includes mathematical modelling in analysing gas-exchange measurements/datasets.
- Epidemiology methodology, large healthcare dataset analysis, including mixed-effects statistical models
- Clinical translational research with human volunteers/ patients (including GCP training & ethics applications)
- Opportunity to work in a wet immunology laboratory e.g. for blood and sputum analysis for cell differential cell counts, ELISAs and MSD multi-plex biomarker assays (blood, sputum supernatant) and transcriptome data analysis (e.g. T2-high vs T2- low, before/after treatment in induced-sputum cells and nasal scrape samples).

The student will be embedded within the Respiratory Medicine Unit, NDM and the NIHR Oxford Biomedical Research Centre which has a dedicated Respiratory theme. As a respiratory clinician trainee, they will be able to contribute to the weekly Special Airways (tertiary) Clinic at the JR Hospital. The clinic is very much integrated with clinical research activities.

Some Relevant References

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