Project Details	
Project Code	MRCPHS25Ca Jurkowska
Title	Targeted reprogramming of epigenetic signals for lung regeneration.
Research Theme	Population Health Sciences
Summary	What most of us do naturally and take for granted – the breathing - 500 million people struggle with as they suffer from incurable lung disease. Epigenetic mechanisms control what genes are switched on or off. They get dysregulated by environmental exposures, causing disease. Despite the identification of epigenetic changes in lung diseases, their functional role remains unknown. This project will establish an exciting new technology called epigenetic editing to precisely manipulate epigenetic signals in lung cells. It will probe which epigenetic changes drive disease phenotypes and if their correction will boost cell regeneration, accelerating the discovery of novel treatments.
Description	**Background:** Chronic lung diseases, including asthma, chronic obstructive pulmonary disease and lung fibrosis are one of the most pressing biomedical challenges of our generation. They affect over 540 million people worldwide and cost the UK economy a staggering £188 billion annually. The molecular mechanisms driving lung diseases are poorly understood and there are no effective treatments. Thus, innovative approaches to the discovery of curative therapies are urgently needed to help restore the lung regeneration programs altered in disease and transform patients' lives. To develop new treatments, we need to understand how healthy individuals develop lung diseases and identify suitable targets for drug development. Epigenetic modifications are chemical groups on our genetic information that determine which genes are active and which are shut off. They get dysregulated by environmental exposures causing disease. Excitingly, they can also be manipulated with the potential to cure disease. Thus, epigenetic signalling provides an exciting and largely unexplored level of regulation for the identification of disease-driving events, novel disease regulators, and biomarkers. DNA methylation is a key epigenetic signal used for the control of gene expression. It is introduced at cytosine residues by DNA methyltransferases and removed by DNA demethylases. Several groups identified global DNA methylation changes in patients with lung diseases, implying the pathogenic role of epigenetic signalling in disease development. However, currently, we do not know which epigenetic alterations are the cause and which are the consequence of the disease process. Therefore, it remains unclear whether epigenetic mechanisms can be targeted for the development of novel therapeutic approaches for lung regeneration. This is because the methodologies for targeted manipulation of epigenetic states are not established in human lung cells. Epigenetic editing is an exciting new technology for precise modification of epigenetic signals. It employs a programable DNA targeting domain (e.g. inactive CRISPR/Cas9) fused to an epigenetic effector domain (e.g. DNA methyltransferase or demethylase), which can be specifically targeted to a desired genomic region to change its epigenetic state, and

	consequently gene expression. It was used to study epigenetic regulation in human cells and animal models and offers exciting prospects for future therapeutic interventions for lung diseases. This innovative project will pioneer the use of this cutting-edge technology in primary human lung cells and organoids. It will develop a versatile platform for understanding how epigenetic signalling drives lung disease development, thereby accelerating the discovery of epigenetic therapeutics and biomarkers for chronic lung diseases. **Aims:** Our group works collaboratively with stakeholders from different sectors to determine how epigenetic dysregulation drives the development of lung diseases and harness this information to develop curative therapies. This PhD project will develop the epigenetic editing technology for use in primary lung cells to understand which epigenetic changes drive disease phenotypes and if their correction will boost the regeneration capacity of lung cells. Objectives: Objective 1: To develop and validate our innovative epigenetic editing tools for locus-specific rewriting of epigenetic signals in human lung cells. Objective 2: To apply these tools to introduce aberrant epigenetic changes (identified by us from patient profiling) at selected genomic regions and examine their functional relevance in driving lung disease phenotypes (focusing on cell regeneration). Using human cell lines, we have already developed combinations of epigenetic domains for sustained activation or repression of target genes upon transient delivery. As primary human lung cells are difficult to transfect but can be efficiently transduced, we will establish epigenetic editing using viral vectors and novel aptamer-based technology for the co-delivery of epigenetic editing domains. After technology establishment, we will demonstrate its power and versality. Using high-resolution epigenetic profiling, we identified numerous sites within the genome severely disrupted in chronic lung diseases. This project will test the functional relevance of these alterations. We will introduce specific epigenetic changes at selected regions in lung cells, model what we observed in patient samples, and examine their impact on driving gene expression changes. Through this innovative approach, we will determine which sites play a causal role in lung disease development and therefore provide the most promising targets for interventions and drug development. **Ownership and co-creation of the project by the student:** The exact project will be co-designed together with the student. The student will be able to steer the direction of the project, drive the selection of the best epigenetic tools and cloning strategies, as well as shape the selection of the most interesting targets and disease contexts for functional validation. **Innovation:** Our group pioneered the use of cell-type resolved epigenetic profiling across disease stages for the identification of novel disease regulators. The innovative aspect of this studentship is the application of epigenetic editing to lung diseases, as this powerful technology has not yet been

	applied to primary lung cells. Thus, this project will deliver a step-change approach for future identification and validation of epigenetic therapeutics and biomarkers for chronic lung diseases.
Supervisory Team	
Lead Supervisor	
Name	Dr Renata Jurkowska
Affiliation	Cardiff
College/Faculty	College of Biomedical and Life Sciences
Department/School	School of Biosciences / Biomedicine Division
Email Address	jurkowskar@cardiff.ac.uk
Co-Supervisor 1	
Name	Dr Tomasz Jurkowski
Affiliation	Cardiff
College/Faculty	College of Biomedical and Life Sciences
Department/School	School of Biosciences / Molecular Biosciences Division
Co-Supervisor 2	
Name	Professor Christopher Scotton
Affiliation	Exeter
College/Faculty	Exeter University Medical School
Department/School	Institute of Biomedical and Clinical Science
Co-Supervisor 3	
Name	
Affiliation	
College/Faculty	
Department/School	