Project Description

Abstract:
This PhD study will analyse epigenomic data sets obtained from tissues of mice exposed to defined aerosol mixtures representative for indoor and outdoor air pollution, and single pollutants with high toxicity potential. Large data sets obtained using the Infinium mouse methylation beadchip platform will be obtained from brain and other tissues in mouse models carrying a stress reporter. The hypothesis will be tested that epigenetic changes that occur in response to stress pathways activated by environmental exposures, constitute a record of exposures that can be predictive of health risk. We will compare changes in DNA methylation and transcription in wild type and mouse models for Alzheimer's Disease to test for increased susceptibility to signaling pathways as well as modelling for 'epigenetic age' acceleration in our environmental exposure stress genomic data and controls[1,2,3]. The PhD study will focus on the role of epigenetics in the environmental impact on health[4], and the development of AI methods for epigenetics[5] to identify biomarkers for environmental risk leading to earlier diagnostics and treatments.

Introduction:
Globally, outdoor and indoor air pollution is responsible for nearly 7 million deaths annually and is one of the leading risk factors for disease burden[6.] While the health hazards of many compounds in air pollution have yet to be untangled, atmospheric fine particulate matter (e.g. PM2.5) is estimated to cause 400,000 deaths a year across Europe from lung disease, cancer, and aggravation of chronic conditions such as cardiovascular disease and neurodegenerative disorders. Its toxic effects include inflammation, oxidative stress and DNA damage. Exposure is also associated with epigenetic changes in the chemical modifications on the DNA and histone proteins, which can affect gene regulation and can be stably maintained even in the absence of alterations to the genetic information in the genome. More knowledge of the epigenetic changes in DNA methylation resulting from environmental exposure is emerging but our understanding of the mechanisms is limited as to how these epigenetic changes occur and how they may facilitate persistent cell trait changes associated with chronic diseases[1].

Research Challenge:
A research question is whether a record of environmental exposures can be identified within the epigenetic marks across the genome, the epigenome. We aim to derive epigenetic exposure profiles that can be used as biomarkers for past exposure and are predictive of disease risk. To increase mechanistic insight into the pathways involved, we also aim to investigate the possible links between such epigenetic changes, signalling pathways, and alterations in gene expression, cell fate or function that may increase disease susceptibility. Several human air pollution studies to date have shown various epigenetic alterations without apparent agreement regarding the pathways involved. This is likely due to confounding differences in genetic background of populations, combined with differences in pollution sources of uncharacterised composition.

Data & Methodology:
Integrative bioinformatics analysis of epigenome methylation changes with gene expression and other data (genetics, blood markers and histology) in mouse models is likely to be more sensitive and identify mechanisms that are conserved and relevant in human[1].
The project will analyse epigenomic and transcriptomic data previously generated in our lab from dissected brain tissues (including hippocampus), liver, and heart. These are derived from mice models exposed to woodsmoke or other pollutants, by our collaborators at the University of Dundee and the University of Eastern Finland. Tissues carry reporters for oxidative stress, and/or include experiments in mouse models carrying either the FAD or APP mutations with susceptibility for Alzheimer disease.

Data sets from defined exposure conditions to pollution sources, and additional correlations with gene expression and stress pathways and other data sets will be used in integrative multimodal analyses combining computational bioinformatics and machine learning where appropriate (e.g. Lasso/Random Forest). Knowledge database translation of mouse pathways analyses to human

epigenome models will be performed. Evaluation of epigenetic profile changes for a range of pollution exposure sources will require a combination of manual feature engineering and machine learning or deep learning models in human multiomic data sets. Adapting findings from mouse and human data sets and evaluation against existing disease and ageing gene neural networks will be employed to identify epigenetic profile biomarkers with potential for evaluating disease risk.

This collaborative study of the mechanistic toxicology of pollutant exposures on mouse brain and other tissues and human cognitive function, offers multidisciplinary training opportunities in biomedical and clinical (toxicology, inflammation, cardiovascular, neuroscience and cognition sciences) and environmental aerosol science. It offers training in epigenetics, genomics and gene expression analyses (infinium methylation array, and RNA seq), and will build on wider bioinformatics research, human public data sets and CTP training in Biomedical AI. This study will analyse primary data from mouse and secondary public data. The animal and human experiments were covered by ethical licences in the labs of origin.

Expected Outcome and Impact:
This project uses the mouse model to correlate many controlled exposure conditions to defined air pollution mixtures with epigenetic changes in stress responsive tissues. It is not possible to do this in humans, but the PhD project will also study human exposures. The mouse models will facilitate the identification of epigenetic changes that may be more difficult to detect in humans where there are more confounding factors.
This PhD project will use mouse model and informatics-based approaches to unravel disease mechanisms of the impact of pollution that are conserved between mouse and human. Ultimately, based on these epigenetic profiles, we aim to develop human biomarkers that can stratify individuals according to prior exposure levels and health risk, and tailor treatments in patients to their epigenetic profiles, which we hypothesise can influence their responsiveness to signaling pathways.

References:
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6. IHME, Global Burden of Disease Study (2019) – processed by Our World in Data.

Collaborator text box
The data sets studied in this PhD project will be generated from exposure experiments in Dundee and Finland using stress reporter mouse models and Alzheimer’s disease mouse models. The extensive data sets we generated are unique, as the experiments used reproducible pollution mixtures produced by aerosol scientists, reporter mice used in controlled exposures by

toxicologists, and tissues dissected and processed for epigenomic and gene expression analyses by epigeneticists.
This project requires the Dundee expert in toxicology and stress signaling pathways to advise on data interpretation of environmental stress responses across the range of experiments. The project requires the expertise of the Edinburgh first supervisor in epigenetics and gene expression for the interpretation and testing of epigenetic models. The second Edinburgh supervisor will contribute extensive bioinformatics experience as well as mouse brain expertise. The Edinburgh first supervisor, who is a PGR Director, also brings extensive supervision expertise from >20 PhD students, receiving 13 Supervisor of the Year nominations in since 2020. This PhD project is a Cross-Institutional (Edinburgh and Dundee) and international collaboration with the University of East Finland for the mouse exposure experiments. The student will become part of a wider UKRI NERC consortium network of the Universities of Manchester, Birmingham, York, Imperial College, Dundee and Edinburgh. This will offer further training and meetings to present work.
This PhD project aims to go beyond computational bioinformatics analyses to develop an AI based integrative interpretation across complex mouse and human data sets in comparison with epigenetic ageing models and Alzheimer's models. It will benefit from bioinformatics AI expertise from the AI-CDT, from which we would invite an additional supervisor, as well as within the Edinburgh Epigenetics network, of which the Edinburgh primary supervisor is the co-organiser.

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