**LEICESTER LIFESTYLE AND HEALTH RESEARCH GROUP**

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| **First Supervisor** | Professor Tom Yates |
| **School/Department** | Diabetes Research Centre, College of Life Sciences |
| **Email**  | Ty20@le.ac.uk |

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| **Second Supervisor** | Thong Huy Cao |
| **School/Department** | Cardiovascular Sciences, College of Life Sciences |
| **Email**  | tch10@le.ac.uk |

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| **Additional Supervisor** | **Leong Loke Ng** Cardiovascular Sciences, College of Life Sciences, lln1@la.ac.uk |

**Section 2 – *Project Information***

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| **Project Title** | **Ethnic differences in response to breaking sitting behaviour: harnessing the proteome for new mechanistic insights.** |
| **Project Summary**  |
| **Project Highlights:**

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| 1.  | Application of mass spectrometry to identify the expression of proteins that differ between white Europeans and South Asians in response to breaking prolonged sitting time. |
| 2.  | Identification of the most biologically plausible proteins that provide new mechanistic or therapeutic insights, with validation against external experimental datasets. |
| 3.  | Measurement of validated proteins and their metabolic effects within Leicester cohorts to investigate the dose-response associations with physical activity and sedentary behaviour in different ethnic groups. |

***Aim:*** To identify and validate novel proteins that will help elucidate mechanisms underpinning different clinical responses to breaking prolonged sitting between ethnic groups by investigation of the plasma proteome using untargeted and targeted omics analyses. This will help personalise and optimise the use of such interventions in the future and suggest novel therapeutic biotargets.***Background:*** People are sitting more and moving less than ever before. Research pioneered in Leicester has demonstrated that simple strategies for breaking prolonged sitting, such as 5 minutes of light-walking every half hour, improve metabolic health [1], with absolute and relative responses greater in South Asian populations relative to White Europeans [2, 3]. As South Asian populations are at high risk of developing cardiometabolic disease and have high levels of physical inactivity, simple interventions to break prolonged sitting have important therapeutic potential. However, mechanisms underpinning ethnic differences have not been elucidated, limiting possibilities for optimising/personalising interventions in the future. There is great potential within the NIHR Leicester BRC to combine our USP in physical activity (Lifestyle theme) with expertise in precision medicine and multi-omic methods (Cardiovascular theme) [4, 5, 6, 7] to investigate why different populations respond differently to lifestyle interventions. This PhD application is designed to harness this potential.***Methods:*** The PhD will encompass three work packages. **Year 1: Identification:** Using blood samples from a trial investigating ethnic differences in response to breaking prolonged sitting [2], the supervisors have already collaborated on a mass spectrometry analysis to generate pilot data. Preliminary analysis confirmed several novel proteins, linked to muscle function and fat oxidation, respond differently between ethnic groups. The student will reprocess this existing mass spectrometry data resource through new spectral libraries, applying novel denoising bioinformatics approaches to identify a full list of proteins which respond differently to breaking prolonged sitting between white Europeans and South Asians. **Year 1-2: Validation:** Topological pathway analysis (TPA), weighted co-expression network analysis, and protein-interaction analyses will be used to refine the list of proteins to those that are biologically plausible with potential to elucidate mechanisms or provide novel therapeutic targets. The student will develop targeted assays using liquid chromatography tandem mass spectrometry to validate shortlisted proteins and appropriate metabolites, using blood samples available from similarly designed interventions [3]. **Year 2-3: Application:** The student will measure validated protein levels within our rigorously phenotyped cohorts, working with our statisticians to examine the dose-response association with markers of cardiometabolic health and physical activity/sitting time within different ethnic groups. ***Expected outcomes and impact:*** This studentship will identify and validate novel proteins that will help elucidate mechanisms underpinning different clinical responses to breaking prolonged sitting between ethnic groups. This will help personalise and optimise the use of such interventions in the future and suggest novel therapeutic biotargets.  |
| **References** |
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