**University of Leicester**

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| **Project Reference** | BRC Studentships |

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| **First Supervisor** | ​Dr David Adlam​ |
| **School/Department** | Cardiovascular Sciences​ |
| **Email** | ​[da134@le.ac.uk](mailto:da134@le.ac.uk) |

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| **Second Supervisor** | Dr Tom Webb |
| **School/Department** | Cardiovascular Sciences​ |
| **Email** | [tw126@leicester.ac.uk](mailto:tw126@leicester.ac.uk) |

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| **Additional Supervisor** | Dr Charles Solomon​ |

**Section 2 – *Project Information***

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| **Project Title** | ​Investigating the molecular and cellular basis for SCAD​ | |
| **Project Highlights:** | 1. | Novel disease area |
| 2. | Opportunity to learn both informatics and laboratory techniques |
| 3. | Experienced supervisory team |
| **Project Summary** | | |
| **Background**: ​Spontaneous coronary artery dissection (SCAD) is a cause of acute myocardial infarction (MI) predominantly afflicting young to middle-aged women with few typical atherosclerotic risk factors. SCAD is characterised by the presence of blood entering and separating the layers of the coronary arterial wall to form a false lumen. This leads to external compression of the true lumen restricting coronary blood flow and leading to coronary insufficiency and MI. SCAD is influenced by a combination of factors including sex, genetics, and emotional and physical stressors, however, the molecular and cellular mechanisms underlying SCAD pathogenesis remain unknown.  Our recent genome-wide discovery efforts (1, 2) and pilot ‘-OMIC’ analyses in people with SCAD have highlighted a central role for smooth muscle and fibroblast expressed genes that encode proteins required for maintaining the arterial extracellular matrix (ECM).  We hypothesise that:   1. SCAD susceptibility is due to a genetic and molecular predisposition for a weakened arterial wall 2. Exposure to changing hormone levels, such as female sex hormones or stress hormones, further weaken the arterial wall triggering SCAD.   Here, we propose an integrated informatics and experimental study to understand the key pathways regulating arterial ECM integrity in SCAD.​  **Aim:** ​The overall aim of this project is to identify specific ECM components and regulators underlying SCAD pathophysiology. ​  **Research Plan**: The following plan will guide the successful completion of this project .   1. *Large-scale integrative analyses of multi-OMIC data:* The student will perform differential expression analyses, co-expression analyses and pathway enrichment analyses in RNA-seq and proteomic datasets from SCAD patients and controls. These analyses will be integrated with our genetic data and other in-house and publicly available OMIC datasets to identify key mediators of the arterial ECM in SCAD and highlight their potential dysregulation by sex and stress hormones. Newly generated data from section d. will be incorporated to confirm and refine this data. 2. *Validation of In-Silico analyses:* The student will use RT-qPCR and immunological assays to replicate findings from the bioinformatic analyses described in section a. 3. *Effect of sex hormones on ECM gene expression in fibroblasts*: The student will treat fibroblasts and f-SMCs with different milieus of sex hormones and perform RNA-seq. This gene expression data will be incorporated into the analysis performed in section a. 4. *Investigation of cell behavior:* The student will compare cellular phenotypes such as proliferation, migration and apoptosis and ECM production in fibroblasts collected from SCAD and control fibroblasts. The same experiments will also be performed in fibroblasts transdifferentiated into smooth muscle cells (f-SMCs). The effect of siRNA knockdown or overexpression of genes identified in section a. and validated in section b. will also be tested to provide insight into how specific mediators of the arterial ECM regulate cell behaviour relevant to SCAD pathophysiology. Specific hormones highlighted in sections a. and c. will be incorporated into these experiments to determine their additive effects on phenotype.   The supervisory team has experience in the described techniques and full training will be provided to the student.  **Expected outcomes and impact:** ​This study will contribute new understanding into the pathogenic mechanisms and predicators of SCAD. This knowledge will be utilized in future development of better treatment strategies for SCAD.​ | | |
| **References**  1. Carrs et al., Spontaneous Coronary Artery Dissection: Insights on Rare Genetic Variation From Genome Sequencing. Circ Genom Precis Med. 2020;13(6):e003030.  2. Adlam et al., Genome-Wide Association Meta-Analysis of Spontaneous Coronary Artery Dissection Reveals Common Variants and Genes Related to Artery Integrity and Tissue-Mediated Coagulation.” <https://doi.org/10.1101/2022.07.05.22277238>. | | |