**University of Leicester**

**BBSRC MIBTP Studentship Project 2024-5 entry.**

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| **Project Reference** |  |

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**Section 2 – *Project Information***

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| **Project Title** | **The Role of Reactive Sulfur Species in the Ageing Heart**  |
| **Project Summary**  |
| **Background**  Ageing is a natural and complex biological process that involves the gradual deterioration of cells, tissues, and organ systems over time, thus leading to an increased susceptibility to diseases and mortality. Aging is a prominent risk factor for cardiovascular diseases (CVD), which is the leading cause of death worldwide. With an ageing society, it is critical to understand the underlying mechanisms of aging heart and develop therapeutic strategies to improve healthy heart (cardiac) ageing and prevent CVD.  Cellular oxidative stress is highly correlated with the ageing. While this has classically been associated with reactive oxygen species (ROS), recent work by our group and others indicate that reactive sulfur species (RSS) are endogenously produced and abundant in cells and tissues that may mediate and/or mitigate cellular oxidative stress (1). As this field is still emerging, much is not known about the cellular effects of RSS. For example, RSS can function as antioxidants in some scenarios, but can be potent cellular oxidants in other conditions.   DNA methylation, which largely controls cellular identity and therefore function, is also altered during the ageing process. In fact, cellular ageing is measured by DNA methylation levels. Thus, we are interested in discovering mechanisms of how ageing results in DNA methylation changes. Dr Switzer is a chemist who has recently discovered that oxidative stress, in the form of nitric oxide, results in genome wide changes in DNA methylation (2). Therefore, if RSS behave as antioxidants, they could be beneficial in healthy ageing. However, if RSS act as oxidants, then their generation may result in accelerated cellular ageing.   Prof Madhani is a cardiovascular pharmacologist and has recently demonstrated that cardiac cells contain high levels of RSS (3). Dr Switzer’s research is focused on RSS cellular chemistry and signalling and has also published that RSS can be either potent cellular oxidants or antioxidants (4). Therefore, we know that RSS is present in cardiac cells, but whether they have the potential to be either pro- or anti-ageing remains to be elucidated. Therefore, this multi-disciplinary project will incorporate chemistry and cardiac pharmacology and physiology to decipher the underlying mechanisms and role of RSS on cardiac cell ageing. We will utilise this information to identify and examine the pre-clinical efficacy of novel compounds to elicit healthy heart ageing.    **Objectives** This project will determine the effect of different reactive sulfur species (RSS) on cardiac ageing as measured by DNA methylation, with a long-term goal of developing novel therapies for healthy heart ageing.   **Methods** To directly measure the effect of RSS on cardiac cell ageing, human cardiac cell lines and primary murine cardiac cells will be cultured and treated with various RSS donors or transfected with either RSS-producing gene expression plasmids or silencing RNA. Cellular RSS will be measured by multiple advanced techniques, including live cell imaging, HPLC and LC-MS. DNA isolation and methylation measurements will be determined to calculate the cellular age, requiring large-scale data analyses. To determine the effects of RSS *in vivo*, transgenic mice (to alter RSS production and/or models of ageing) will be used. Established *ex vivo* and *in vivo* methods will be employed to study cardiac function in the transgenic mice. Additionally, potential drugs will be screened for their ability to improve cardiac cell ageing initially in human cell lines and translated to mice.**Techniques that will be undertaken during the project*** In vitro cell culture of human and murine cardiomyocyte (primary cells and cell lines)
* In vitro transgene expression
* In vivo and ex vivo transgenic mouse models of cardiac function
* Live cell imaging of RSS and other cellular parameters
* Biochemical characterisation of RSS (HPLC, LC-MS/MS)
* DNA methylation sequencing and bioinformatic analysis
* Gene expression analysis (mRNA-seq)
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| **References** |
| 1. C. H. Switzer, S. Kasamatsu, H. Ihara, P. Eaton, SOD1 is an essential H2S detoxifying enzyme. Proceedings of the National Academy of Sciences 120, e2205044120 (2023). 2. C. H. Switzer, H.-J. Cho, R. Eykyn Thomas, P. Lavender, P. Eaton, NOS2 and S-nitrosothiol signaling induces DNA hypomethylation and LINE-1 retrotransposon expression. Proceedings of the National Academy of Sciences 119, e2200022119 (2022). 3. K. Griffiths et al., Cysteine hydropersulfide reduces lipid peroxidation and protects against myocardial ischaemia-reperfusion injury - Are endogenous persulfides mediators of ischaemic preconditioning? Redox Biology 60, 102605 (2023). 4. C. H. Switzer, J. M. Fukuto, The antioxidant and oxidant properties of hydropersulfides (RSSH) and polysulfide species. Redox Biology 57, 102486 (2022).  |

**To apply please refer to**

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