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Section 2 – *Project Information*

Project Title	MLTC related chromatin remodelling and dysregulated iron homeostasis as the basis for the Obesity Paradox

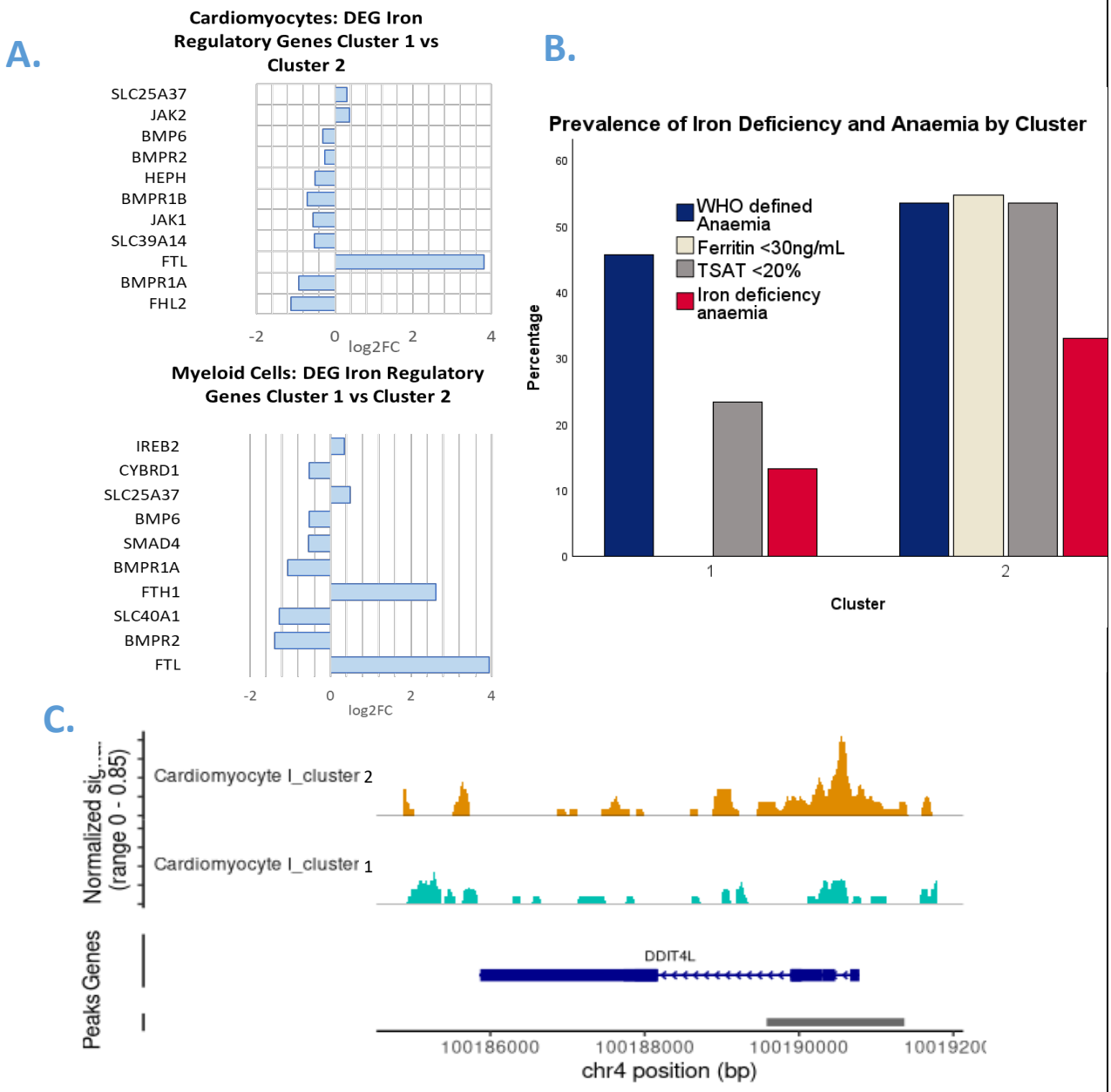
Project Summary

Organ injury is common following cardiac surgery, where it contributes to excess mortality, delayed recovery, progression of long-term conditions, poor quality of life, and increased use of healthcare resources. People who are overweight or who have mild obesity demonstrate reduced susceptibility to organ injury and its complications after cardiac surgery. (1) In contrast, people with lower (<25) and very high (>35) Body Mass Index (BMI) demonstrate increased levels of organ injury and death after surgery. This is referred to as the obesity paradox.

People with lower (<25) and very high (>35) BMIs also demonstrate increased prevalence of Multiple Long-term Conditions (MLTC) or multimorbidity. It follows that the obesity paradox may simply reflect reverse causation, whereby those at the extremes of BMI are sicker at the outset. However, the mechanisms by which MLTC increase susceptibility to organ injury is unknown. Understanding these mechanisms will provide new insight into organ injury and the obesity paradox, and may identify novel therapeutic targets for organ protection.

Our previous research suggests that accelerated Biological Ageing associated with Multiple Long-term Conditions (MLTC) at lower (<25) and very high (>35) BMIs may underlie our observations. (2) Biological ageing refers to a cluster of 14 cellular processes (reviewed in (22)) common to many age-related diseases. We have also shown that myocardial biopsies from people with MLTC demonstrate the hallmarks of biological ageing. (3) Next, we demonstrated that accelerated biological ageing in MLTC is characterised by T cell exhaustion, dysregulated tissue resident macrophage activation, dedifferentiated cardiomyocytes and increase susceptibility to acute myocardial and renal injury. (4) Finally, in unpublished work, we demonstrated that accelerated biological ageing in cardiomyocytes was associated with attenuation of the iron restriction response, systemic iron deficiency, and increased chromatin accessibility for the DDIT4L promoter (unpublished, **Figure 1**), a stress response gene expressed in cardiomyopathy, and a regulator of dedifferentiation.(5). Cardiomyocyte dedifferentiation in the setting of iron deficiency is analogous to hibernating myocardium that shows increased susceptibility to ischaemia reperfusion.(40) This provides a plausible mechanism for the increased susceptibility to myocardial injury we observed in the accelerated ageing/ inflammageing group, (26) and also the obesity paradox.

Figure 1. A. Differentially expressed iron restriction genes in cardiomyocytes and myeloid cells from snRNAseq analyses of myocardial biopsies from **Cluster 1**: Less advanced biological ageing versus **Cluster 2**: More advanced Biological Ageing (Inflammageing), data extracted from (4). **B.** Systemic iron indices in plasma from Clusters 1&2. **C.** Combined snRNAseq/ ATACseq analyses of Cardiomyocytes in Cluster 1 versus Cluster 2 (unpublished), demonstrating differences in chromatin accessibility to the promoter for DDIT4L.
These findings lead us to hypothesise that the Obesity Paradox can be explained by changes in chromatin



accessibility and cellular iron metabolism associated with accelerated biological ageing in MLTC at the extremes of BMI.

In addition, recently, the Lancet Commission on the Definition and Diagnostic Criteria of Clinical Obesity published a revised definition of Obesity that includes the presence of increased adiposity (elevated hip:waist ratio, elevated BMI plus evidence of reduced organ or tissue function due to obesity (ie, signs, symptoms, or diagnostic tests showing abnormalities in the function of one or more tissue or organ system). We propose to use this revised definition in a sensitivity analysis, alongside BMI only based definitions to test our primary hypotheses.

This project will use existing clinical data sets to investigate the interactions between MLTC, obesity, susceptibility to organ injury, and linked RNAseq/ ATACseq datasets to investigate the role of epigenetics in these interactions, and preclinical models and genomic datasets (UK Biobank) to establish causation.

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