Background
Ischaemia occurs in many pathological situations when blood supply to an organ is shut off, such as during a heart attack or organ transplantation. Furthermore, restoration of blood supply to the organs is associated with clinically critical damage. Over the past few years the Saeb-Parsy, Murphy, Frezza and Krieg labs in Cambridge have collaborated on this area with a focus on understanding the mechanisms of damage and on developing new therapies. This work has led to breakthroughs in understanding how the rapid changes in mitochondrial metabolism contributes to ischaemia-reperfusion injury and to the development of novel therapeutic approaches (eg malonate, MitoSNO, [1-3]). In this work we have been able to acquire unique data sets on the levels of tissue metabolites and transcriptomes in mouse, pig and human heart and kidneys at all stages of ischaemia and reperfusion, utilising a diverse range of in vivo and ex vivo experimental models. These data sets provide an unprecedented opportunity to model the changes in metabolism and gene expression at all stages of ischaemia and reperfusion and to determine similarities and differences between mouse, pig and human tissues. This modelling will be done by the postdoc under the leadership of Dr Irene Papatheodorou, with the post doc expected to work closely with Saeb-Parsy/Murphy/Frezza/Krieg labs. From this modelling we will be able to infer potential sites for therapeutic intervention, and also to develop new prognostic markers. Importantly, the modelling will also inform new biological experiments and will be part of an ongoing collaboration between the medical school and the EBI in which modelling informs the design of new experiments to examine the efficacy of therapeutic interventions.

Aim 1: Model metabolic changes in human, mouse, pig and link to gene expression
Joint metabolomics and transcriptomics data analysis of paired samples will be performed using statistical and unstructured methods (enrichment analysis, blocs data integration, etc), as well as mechanistic modelling, such as constraints based metabolic model [4]. Signatures of transcriptomics and metabolomics data obtained from paired samples will be integrated. For the purely statistical data integration, data can be analyzed as usually for both Metabolomics and Transcriptomics, and then integrated at the level of data matrices through different methods. For a mechanistic understanding of underlying phenomena however, a more biologically constrained approach will be employed. On constrained based analysis, both transcriptomics and metabolomics data have been used in the past as restrictions (in the nature of constrained metabolic models being linear problems) through a number of different methods [5, 6] to further characterise the solution space of metabolic phenotypes,
starting from tissue specific models [7] which based on community-based reconstructions of human metabolism [8] (which has received updates since its original version in 2007).

**Aim 2: Identify metabolic causes of pathological phenotypes and discover diagnostic biomarkers**

Data analysis of paired samples from control ‘normoxic’ and ischaemic tissues from various disease models, such as myocardial infarction, organ transplantation and stroke, will be used to identify signatures of metabolite expression, as well as signatures of gene expression using classification methods. Signatures of metabolite expression would be used to identify links to pathology of the affected tissues, whereas gene expression signatures would be suggestive of potential diagnostic markers.

**Aim 3: What are the metabolic and transcriptomic changes after therapeutic intervention?**

We will explore differences between healthy and diseased tissue, before or after therapeutic intervention such as those described above [1, 2] both in metabolomics and transcriptomics data sets. Metabolomics data analysis will be powered by cloud deployable and scalable infrastructures that provide state of the art tools, such as Workflow4Metabolomics and PhenoMeNal; Transcriptomics data analysis will be powered by the iRAP pipeline, developed at EBI.

**References**

[1] Cardioprotection by S-nitrosation of a cysteine switch on mitochondrial complex I

[2] Ischaemic accumulation of succinate controls reperfusion injury through mitochondrial ROS

[3] A unifying mechanism for mitochondrial superoxide production during ischemia-reperfusion injury
Edward T. Chouchani, Victoria R. Pell, Andrew M. James, Lorraine M. Work, Kourosh Saeb-Parsy, Christian Frezza, Thomas Krieg and Michael P. Murphy
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