Identification of novel anti-obesity therapies stimulating brown/beige adipocytes

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Background – An important Biomedical Problem and a new original approach.

Obesity and associated disorders are a major and increasing problem for the western world, for which there is an urgent need to develop novel therapies. Brown adipose tissue (BAT) is a newly "rediscovered" key metabolically active organ that generates heat to maintain body temperature. Accordingly, it has been established that BAT protects against diet-induced obesity in mice and that in humans levels of detectable BAT are inversely correlated with bodyweight, fat mass and markers of metabolic health (Ouellet et al., 2011). Thus, defining the regulation of BAT is a promising avenue to develop novel therapies for metabolic disorders (Whittle et al. 2011). Recent evidence suggests that human BAT is more similar to an intermediate cell population observed in mice, termed beige adipocytes (Wu et al., 2012). These are brown-like thermogenic cells, which are recruited following cold-exposure or treatment with PPARγ agonists in traditionally white fat depots. These findings suggest that **adult humans may retain the capacity to recruit additional thermogenic capacity in a similar manner, given the right stimulus.**

The TVP lab has a world-leading expertise on BAT and Vidal-Puig is an associate faculty at the Sanger Institute. In collaboration with Bill Skarnes' group they have succeed at generating and isolating adipocytes of brown/beige lineages from murine and human pluripotent stem cell-lines. These adipocytes are already available in large amounts, providing a unique resource to perform systematic functional studies and a thorough characterization using –omics analyses. On-going characterization of these cells at the TVP lab includes RNA-seq-based transcriptomics (at WTSI), proteomics, and metabolomics/lipidomics.

Specific Objective: In this project, we propose to build a mathematical model of the key molecular mechanisms governing BAT generation from murine and human stem cells and the thermogenic activation of the mature brown adipocytes. We will use these models to identify candidate targets to develop novel therapeutics to induce BAT and thereby treat metabolic disorders. The experience gained on this will be **transferable** and applicable to other metabolic disorders.

Research plan

In a ***first phase,*** the fellow will develop an integrated network model of signal transduction, gene regulation and metabolism in adipocytes. This model will be built using the transcriptomics, metabolomics, and proteomics data generated by TVP and BS lab along with prior knowledge of the underlying molecular pathways obtained from repositories at EBI (e.g. Reactome) and elsewhere. While well-established mathematical models for individual levels exist, integrating these different layers is an important challenge (Gonçalves et al. 2013). The JSR group develops methods for these integrated models that will be applied here.

In terms of **signal transduction**, we will focus initially on Bone Morphogenic Proteins (BMPs). BMPs have been implicated in brown adipose tissue development (Tseng et al., 2008) and the TVP lab has recently discovered a key role of BMP8b in the regulation of mature BAT thermogenesis (Whittle et al. 2012). Previous attempts to target BAT therapeutically have failed due to a lack of tissue specificity but BMP8B is able to specifically increase the adrenergic sensitivity of mature brown adipocytes, which is the major mediator of both their recruitment and thermogenic activity. The TVP lab is undertaking the first ever unbiased phosphoproteomic screen of brown and white adipocytes following BMP treatment and/or norepinephrine stimulation. This study aims to identify intracellular signalling pathways unique to BAT that may be targeted by drugs. The fellow

will work in the JSR group to perform computational analyses on phosphoproteomic datasets provided by TVP. This model will inform future in vitro screens.

In a **second phase**, the fellow will use the model to identify novel pharmaceutical strategies to induce BAT generation. The model will be used to evaluate *in silico* the potential effect of drugs on adipocytes. In combination with this model and the existing data, we will use available data sets describing gene expression upon drug treatment. It has been shown that gene expression data of this sort provides insight into a drug's mode of action and can suggest novel actions (Iorio et al. 2013). Methods developed in the JSR group (Pacini et al. 2013) and elsewhere to leverage this data will be used. The best candidate molecules will be applied to the stem cell models to confirm their capacity to induce brown adipogenesis *in vitro*. Experiments will be performed with the support of Stefania Carobbio and Barry Rosen at WTSI.

In **summary**, the fellow will (i) build a mechanistic model of Brown fat development and more specifically will investigate the role of BMP8-induced metabolism and regulation in adipocytes, (ii) use it to propose novel therapeutic interventions to induce and activate brown adipocytes, and (iii) test these hypothesis on stem cell models.

This project will provide the fellow **state of the art interdisciplinary training** in the analysis and integration of different 'omics' data, network modelling and systems pharmacology, as well as in stem cells, adipocyte's biology and brown fat physiology.

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