Brown Adipose Tissue Activation in Humans

Section 1 – Project Details:

Rationale:

Obesity is a leading global health concern, with no effective drug treatments currently available. Brown adipose tissue (BAT) is a major effector of adaptive thermogenesis and an attractive anti-obesity drug target [1]. It is a highly metabolically active organ which utilises glucose and free fatty acids and is able to release chemical energy efficiently as heat by uncoupling mitochondrial respiration from ATP production [2]. Increased BAT activity results in raised energy expenditure and improves glycaemic control and blood lipid profile [3].

In recent years, following its rediscovery in adult humans [4-8], BAT has been the focus of intense research and the total amount of this tissue in adult humans has recently been revised upwards [9]. However, replication of the promising results from animal studies have been slow [10]. This is due, in part, to difficulties measuring BAT activity directly in humans. Its anatomical position, close to major vessels, makes it difficult to routinely biopsy, resulting in imaging being the preferred method of BAT quantification. The standard method of BAT imaging remains positron emission tomography-computed tomography (PET-CT) which exposes participants to significant radiation doses and is, therefore, not suitable for repeated measures, or studies with large numbers of healthy volunteers or children. PET-CT is also limited to making measurements in fasted subjects [11].

An alternative imaging technique, infrared thermography (IRT), makes use of the heat generating properties of BAT and the relatively superficial position of the supraclavicular depot, one of the largest BAT depots in adults [7]. Using IRT, several research groups have shown a specific rise in supraclavicular temperature (TSCR) following introduction of a cool stimulus [12-15]. IRT has the advantage of being able to measure real-time activation and can be used to gather repeated measures in large numbers of subjects irrespective of age and nutritional status. We have recently shown there is a good correlation between the amount of glucose taken up within supraclavicular BAT with both baseline and peak TSCR relative to a reference region. Furthermore, participants with greater BAT activity show greater overlap between the glucose uptake and TSCR hotspots (R²=0.61, p=0.02). We are uniquely placed to utilise these IRT techniques in patients to establish whether dietary intake and/or changes in neuro-endocrine status linked to improved energy balance are mediated by changes in BAT function.

Aims and methodology

The primary objective of this project is to study, for the first time, the dynamic changes in BAT in the following clinical scenarios:

A. Morbidly obese subjects undergoing substantial weight loss as a result of lifestyle interventions and bariatric surgery
B. Patients with hyperprolactinaemia before and after treatment with dopamine agonists
C. Patients with Non-Alcoholic Fatty Liver Disease (NAFLD)
D. Patients presenting to hospital with acute pyrexial illnesses and during their convalescence
These seminal studies will generate novel data regarding the association between human BAT activation and important clinical disorders and pave the way for future large scale interventional studies.

In all cases, participants (n=20 in each of the 4 groups) will undergo IRT imaging of their BAT. This involves the participant sitting in front of a thermal imaging camera with their neck and shoulders exposed for a maximum of 45 minutes. During this time, a series of digital images are taken, in the basal state, and after one of their hands is cooled to 17°C. A detailed research protocol has been developed submitted for ethical and NHS R&D approval. In summary, participants will have thermal imaging performed as follows:

(A) In the morbid obesity/bariatric surgery group - twice (at least 2-months apart) before bariatric surgery and 6 and 12 months after bariatric surgery.
(B) With hyperprolactinaemia before they commence standard, clinically-indicated treatment with dopamine agonists and for up to 12-months after treatment is initiated.
(C) With a pyrexial illness, within 12-hours of presentation to the acute medical unit and repeat imaging once they have been apyrexial for at least 48 hours.
(D) With NAFLD at recruitment and at the end of each of their routine gastroenterology/hepatology follow-up appointments over the following 12 months.

A sample size of n=20 for each of the pilot study groups is sufficient to demonstrate the likely magnitude of changes and whether there is a prima-facie association with the severity of pyrexial illness and/or sepsis and/or bariatric surgery or weight loss. All statistics will be performed using PASW (formerly known as SPSS: v 17.02, IBM, Chicago, USA) software for Windows and our validated thermal imaging software.

Benefits and suitability as a PhD Project:
- Joint supervision across Divisions in School of Medicine
- Training in state-of-the-art techniques of BAT measurement
- Training and experience in research involving human participants in a clinical setting
- Project spanning basic science and clinical areas
- Opportunity to work within leading BAT research group with successful track-record of innovation and supervision
- Previous studies have confirmed robustness of methodology. NHS Ethics and R&D application already submitted, so project “ready-to-go”

Key References:


Section 2 – Training Provision:

Maximum of 250 words. Please detail the training provision that will be made available to the student.

The two Divisions hosting this PhD have extensive experience in mentoring and supervising postgraduate research students. Basic scientists and clinical academics work in close partnership and PhD students are supported as integral members of the team. Following an induction period, the student will have the opportunity to attend University of Nottingham courses that cover Research Methods, Research Governance, and Statistical methods. The PhD student will undertake Good Clinical Practice (GCP) training, allowing them to take an active role in research projects involving NHS patients. Bespoke training will be given in all the methodologies required for the specific project and the student will become an expert in the use of IRT to image BAT. The project will involve considerable patient contact in a clinical setting, and students will be given training in communications skills, the explanation of the studies and in receiving informed consent from participants, and management of research within the NHS. In addition to at least weekly progress meetings with their supervisor(s), and monthly documented supervisory meetings as part of the PGR web system, students will have access to a vibrant PGR community including participation in regular seminars and “show-and-tell” events covering a wide range of research projects within both Divisions and the wider School of Medicine.