Exercise as medicine: discovery of novel “exerkines” regulating the health benefits of physical activity

Section 1 – Project Details:

Maximum 800 words, using the following headings

Rationale:

“Exercise as medicine” remains a major health initiative. Yet the mechanism by which exercise promotes these health benefits is poorly understood. A major challenge to this is determining how the major metabolically active tissues such as skeletal muscles, interact with other organ systems (heart, lungs, liver) to trigger these positive adaptations in health to exercise e.g. reducing fat stores, improving heart function. Recently, it has been suggested that contracting muscle may release so called “exercise factors” into the circulation, which act like hormones on other tissues to infer the positive effects of exercise. Despite this proposal, very little is known about these “exercise factors”, how they are made and how they may act on their target tissues. Therefore, the present study will aim to use novel analytical techniques, involving metabolic tracers (alongside proteomics) to help identify these “exercise factors”, determine how (and at what rate) they are made in response to health promoting exercise, and how they interact with numerous health endpoints e.g. insulin sensitivity, blood pressure. If these exercise factors can be positively identified and characterized, this could lead to the development of novel drug targets for promotion and maintenance of health, whilst also having the potential to help combat the development of a number of non-communicable diseases such as diabetes. Moreover the link between basic science and clinical science provided by the supervisory team of Dr Wilkinson and Dr Idris, provides a true potential to generate future income through translation of basic scientific findings to human health interventional strategies.

Aims and methodology:

The overarching aims of this PhD project will be:

i) To detect the temporal appearance of exercise factors in response to endurance training.

ii) To determine the metabolism (synthesis, secretion and tissues of action) of these exercise factors in response to endurance exercise training

iii) To determine the relationship between identified exercise factors and physiological/health related outcomes.

In order to achieve the above aims 10 healthy young men and women (50:50) will undertake 4 weeks endurance exercise training (EET: cycling at 60-70% VO2 max) 3 x times a week. During this training protocol skeletal muscle, adipose tissue and blood will be sampled to assess for the presence of any proposed “exercise factors”. Before and after completion of training, health endpoint measures will be determined (e.g., blood pressures, body composition etc..), to assess for the positive impacts of the exercise training. In addition, each individual will be provided with the stable isotope tracer, deuterium oxide (D2O), throughout the study. D2O is a novel isotopic tracer technique our lab recently pioneered (5 peer-reviewed articles already; 2-6), which allows for dynamic quantification of tissue metabolism in relation to physiological and key clinical outcome (measures key to achieving the project aims). We will use this technique to measure the rate at which any detected “exercise factor” proteins are being made and released in response to the exercise, and which tissues they may be interacting with to promote positive helath outcomes. The combination of stable isotope tracers with proteomics (the large scale detection of proteins
within a biological sample) is becoming an increasingly powerful technique, for determining the dynamics of in vivo metabolism, as many recent example can attest to. By extension, we contend that factors being secreted in response to exercise could be similarly detected in this fashion, and crucially, that this would permit identification of novel exercise factors. As such, the careful design of this protocol will permit us to achieve the aims outlined above, and the information provided through this work will have unique translational potential in terms of health promotion and disease prevention, for example target pharmaceutical manipulation of these factors could be developed into future treatment options for a number of diseases (e.g. diabetes).

Benefits and suitability as a PhD project:
Not only will the PhD student be able to benefit from being situated within one of the world leading research labs for Musculoskeletal Metabolism and Physiology, providing the opportunity to interact and learn from a number of internationally renowned researchers within this field. But this project represents one of the hottest current topics in health and physiological sciences; “exercise mimetics”, and it will no doubt provide the student with the opportunity to lead and contribute to the production of the numerous highly impactful papers emanating from this work. Moreover, the student will have the opportunity to develop skills in a number of different analytical techniques, with OMIcs, bioinformatics and biostatistics being a large part of this. There has been a recent explosion of interest in OMIcs technologies across a wide range of disciplines, therefore these skills will benefit the student no matter what discipline they choose to pursue post PhD, and will therefore provide an excellent platform for the student to develop into an independent researcher in their own right.

Key References:
Section 2 – Training Provision:

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

The host research group is vibrant and has a strong commitment to staff/student development (currently 12 PhD students; 6 basic scientists, 6 CRF’s, 3 postdocs and 3 technicians). Beyond supervisory training they have numerous opportunities: i) N-trans accreditation, ii) a multi-domain researcher development programme (including online learning, face-to-face courses and public engagement), and iii) a vast range of courses (practical, IT, interpersonal skills) available to them. Moreover, they would be housed in an excellent and well-resourced research facility. Our laboratories (400m² purpose-built) are in the Derby located MRC/ARUK Centre for Musculoskeletal Ageing Research and are unique in combining the interrogation of physiology and metabolism with in vivo and ex vivo molecular biology. The application of proteomics within this PhD provides a unique opportunity for training provision in the niche area of biostatistics and bioinformatics. Under the guidance of the supervisors (and collaborative partners) the student will be provided with the opportunity to undertake, learn and develop unique bioinformatic skills relating to the extraction, pre-processing and data analysis of large multivariate data sets. Dr Wilkinson has training in biostatistics and programming for large data sets and will provide supervision of this training. Moreover through already established collaboration with the Universities of Birmingham and Stirling there is excellent scope for training and additional support in proteomics and informatics. The student will leave this PhD with an enviable range of skills ranging from basic physiology and biochemistry, to unique technical skills relating to the application of mass spectrometry, metabolomics and biostatistics to translational medicine.