



RESEARCH SCHOLAR PROGRAM – 2018

SUPERVISOR & PROJECT INFORMATION FORM

Please complete and return, via email only (crems.programs@utoronto.ca) by **November 3rd 2017** (*forms received after this date will not be posted*).

Supervisor Information

Name: Marc G. Jeschke

Email: marc.jeschke@sunnybrook.ca

Degree: M.D., PH.D. SGS Appointment (IMS, IHPME, LMP etc.): IMS

Academic Rank: Professor

Field of Research: Burn injuries

Research Institution Affiliation (if applicable): Sunnybrook Research Institute

Allocation of student contact time (number of hours per week YOU are available to the student for any concerns or to review progress): 3

Project Information

Title: Elucidating the role of carnitine palmitoyltransferase in post-burn adipose browning and hypermetabolism

Description (max 500 words):

Hypermetabolism is a chronic physiological response to severe trauma such as burns and is associated with the cachexia that occurs in advanced cancers and infectious diseases such as tuberculosis and the human immunodeficiency virus (HIV). Trademarks of this phenomenon include increases in resting energy expenditure (REE), supraphysiological nutritional requirements and the systemic wasting of adipose tissue reserves and muscle tissue. Although not understood in its entirety, the hypermetabolic response is thought to be driven primarily by catecholamines, corticosteroids and pro-inflammatory cytokines. Fortunately, interventions exist which lower these mediators and curb the degree of hypermetabolism. These include insulin to restore normoglycemia, beta blockers such as propranolol and anabolic steroids such as oxandrolone. However, while these therapeutic agents can mitigate the damage stemming from a hypermetabolic state, an absolute cure for this condition has eluded researchers.

The preservation of white adipose tissue (WAT) is seen as a valuable strategy to improve patient outcomes in cachexic/hypermetabolic states. Not only does the loss of WAT lead to a decrease in body mass and higher susceptibility to infections and sepsis, but the increased circulation of free fatty acids (FFAs) due to WAT lipolysis leads to the ectopic deposition of fats in organs such as the liver and skeletal muscle, further exacerbating the damage to these tissues and promoting organ dysfunction. The issue of increased lipolysis is compounded by the knowledge that WAT undergoes a browning process following severe burns and during cancer-associated cachexia. This phenotypic switch, whereby adipocytes increase mitochondrial biogenesis and the expression of uncoupling protein 1 (UCP-1), is associated with augmented lipolytic activity and increased systemic energy expenditure. While browning is often regarded as a positive biological phenomenon with the potential to improve outcomes for metabolic disorders such as obesity and diabetes, it is postulated that the conversion of WAT to a beige phenotype during hypermetabolic/cachexic states worsens outcomes and impedes the conservation of body mass. To that effect, therapeutic agents that preserve fat should ameliorate patient wellbeing.

Here, we seek to uncover the role of carnitine palmitoyltransferase (CPT) in the post-burn browning phenomenon. CPT catalyzes the rate-limiting step in the shuttling of long chain fatty acids to the mitochondria for beta-oxidation. Furthermore, its activity appears to be key in the initiation of WAT browning. Using a murine model of burn injury and the CPT inhibitor oxfenicine, we intend to study the activity and expression of CPT in subcutaneous WAT to determine its relationship with browning, UCP-1 and the increased lipolysis seen in animal model and patients. Mitochondrial dynamics will be assessed using a Seahorse XF96 analyzer, in-gel activity assays and Western blots, and the impact of lipolysis and browning studied in downstream organs such as the liver and muscle tissues. We postulate that the rate of CPT activity may be linked to browning and UCP-1 expression and that pharmacological inhibition of the former may improve outcomes after severe burn injury.

If human subjects are involved, have Ethics been obtained?

YES

NO

Application Submitted

N/A

Do you expect this work will be published within the 20 months?

YES

NO

Uncertain

Student's roles and responsibilities (please be specific)

Please indicate who will serve as the student's direct report (PI, PhD student, technician etc...)

Expectations of the student will be to participate in animal experiments, bench work and data processing, the results of which are presented to Dr. Christopher Auger, the direct supervisor of this work. Weekly meetings will be held where the student will report to Dr. Marc, Jeschke, the principal investigator. Previous lab experience (mouse work, Western blotting, PCR), including publications and graduate degrees, will be considered assets.