ERASMUS UNIVERSITEIT ROTTERDAM

Erasmus University Rotterdam, the Netherlands
CSC PhD 2015 Project Description

School/Department:	*Internal Medicine, Erasmus MC*
Project Title:	**Exploring sex differences in regulation of brown adipose tissue activity: A focus on the brain.**
Abstract:	Brown adipose tissue (BAT) is present in animals and humans and this tissue has the unique ability to burn lipids to generate heat. Upon certain stimuli, white adipose tissue (WAT) can also gain BAT-like properties. Activation of BAT and 'browning' of WAT are considered very promising tools to correct obesity and its associated metabolic disorders such as cardiovascular diseases (CVD). Multiple studies show that compared to men, women have more active BAT or 'brown' WAT and lower CVD incidence. A recent study showed that the female sex steroid estradiol induces BAT activity mainly via effects on the hypothalamus, but the exact mechanisms and consequences of this estrogen-CNS-BAT system are largely unknown. Also, a possible differential role of the CNS in control of male and female BAT has not been studied. Cold exposure activates BAT, a process mediated by the CNS. Thus, differences in cold sensitivity might result in differences between male and female BAT. We recently found that women sense cold at higher temperatures than men: females start shivering at higher temperatures than men. <u>The general aim of this research proposal is to untangle the complex interplay between sex steroid hormones, CNS and BAT.</u> For this project, we will study male and female mice with modifications in their sex steroid hormone content and/or sex steroid hormone receptors. In some studies, mice will receive injections with sex steroid hormones in the CNS or in the periphery. Denervation of the BAT depot will be a tool to study the direct CNS-BAT interaction. All mice will be studied under various housing temperatures in metabolic cages to assess energy expenditure. Another part of the project is a human study in which we will determine the association between thermosensitivity and BAT activity in men and women. For this, we will determine BAT glucose uptake of individuals at a temperature close to their shivering temperature. Altogether, this project will teach us why females have more active BAT and what the role of the CNS is in this. All this will, in the end, provide knowledge that is required to develop novel treatments to activate BAT and improve metabolic health.

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Requirements of candidate:	Master degree: Yes Background: We are looking for a candidate who is acknowledged with basic laboratory skills such as real-time PCR, Western blotting and histology. The candidate is willing to work with animals. Although we prefer a candidate who has experience with animal work, this is not a prerequisite. IELTS Grade: 7.0 *(minimal 6.0 per component)* *or* TOEFL: *100 (minimal 20 per component)*
Supervisor information:	Dr. A. Grefhorst a.grefhorst@erasmusmc.nl **Publication list since 2010** 1. van den Beukel JC, **Grefhorst A**, Hoogduijn MJ, Steenbergen J, Mastroberardino PG, Dor FJ, Themmen AP. Women have more potential to induce browning of perirenal adipose tissue than men. *Submitted* 2. van den Berg SH, van den Beukel JC, **Grefhorst A**, Hu C, Themmen AP, Valkema R. Higher prevalence in brown adipose tissue activity in women: due to a different set point of the thermostat? *Submitted* 3. van den Beukel JC, **Grefhorst A**, Quarta C, Steenbergen J, Mastroberardino PG, Lombès M, Delhanty PJ, Mazza R, Pagotto U, van der Lely AJ, Themmen AP. Direct activating effects of adrenocorticotropic hormone (ACTH) on brown adipose tissue are attenuated by corticosterone. FASEB J. *In Press* 4. Toonen EJ, Laskewitz AJ, van Dijk TH, Bleeker A, **Grefhorst A**, Schouten AE, Bastiaanssen EA, Ballak DB, Koenders MI, van Doorn C, van der Vleuten MA, van Lierop MJ, Groen AK, Dokter WH. Glucose Kinetics in the Collagen-Induced Arthritis Model: An All-in-One Model to Assess Both Efficacy and Metabolic Side Effects of Glucocorticoids. PLoS One 2014: 9: e98684 5. Stevanovic DM, **Grefhorst A**, Themmen AP, Popovic V, Holstege J, Haasdijk E, Trajkovic V, van der Lely AJ, Delhanty PJ. Unacylated ghrelin suppresses ghrelin-induced neuronal activity in the hypothalamus and brainstem of male rats. PLoS One 2014: 9: e98180 6. van den Beukel JC, **Grefhorst A**. Interactions between the gut, the brain and brown adipose tissue function. Front. Horm. Res. 2014:

42: 107-122
7. Hijmans BS, **Grefhorst A**, Oosterveer MH, Groen AK. Zonation of glucose and fatty acid metabolism in the liver: Mechanism and metabolic consequences. Biochimie 2014: 96: 121-129
8. van Dijk TH, Laskewitz AJ, **Grefhorst A**, Boer TS, Bloks VW, Kuipers F, Groen AK, Reijngoud DJ. A novel approach to monitor glucose metabolism using stable isotopically labelled glucose in longitudinal studies in mice. Lab Anim. 2013 47: 79-88
9. Delhanty PJ, Huisman M, Baldeon-Rojas LY, van den Berge I, **Grefhorst A**, Abribat T, Leenen PJ, Themmen AP, van der Lely AJ. Des-acyl ghrelin analogs prevent high-fat-diet-induced dysregulation of glucose homeostasis. FASEB J. 2013: 27: 1690-1700
10. van Lierop MJ, Alkema W, Laskewitz AJ, Dijkema R, van der Maaden HM, Smit MJ, Plate R, Conti PG, Jans CG, Timmers CM, van Boeckel CA, Lusher S, McGuire R, van Schaik RC, de Vlieg J, Smeets RL, Hofstra CL, Boots AM, van Duin M, Ingelse BA, Schoonen WG, **Grefhorst A**, van Dijk TH, Kuipers F, Dokter WH. Org 214007-0: A novel non-steroidal selective glucocorticoid receptor modulator with full anti-inflammatory properties and improved therapeutic index. PLoS One 2012: 7: e48385
11. Willart MA, van Nimwegen M, **Grefhorst A**, Hammad H, Moons L, Hoogsteden HC, Lambrecht BN, KleinJan A. Ursodeoxycholic acid suppresses eosinophilic airway inflammation by inhibiting the function of dendritic cells through the nuclear farnesoid X receptor. Allergy 2012: 67: 1501-1510
12. Laskewitz AJ, van Dijk TH, **Grefhorst A**, van Lierop MJ, Havinga R, Schreurs M, Bloks VW, Reijngoud DJ, Dokter WH, Kuipers F, Groen AK. Chronic prednisolone treatment aggravates hyperglycemia in mice fed a high fat diet but does not enforce dietary fat-induced insulin resistance. Endocrinology 2012: 153: 3713-3723
13. **Grefhorst A**, Oosterveer MH, Brufau G, Boesjes M, Kuipers F, Groen AK. Pharmacological LXR activation reduces presence of SR-B1 in liver membranes contributing to LXR-mediated induction of HDL-cholesterol. Atherosclerosis 2012: 222: 382-389
14. **Grefhorst A**, Schreurs M, Oosterveer MH, Cortés VA, Havinga R, Herling AW, Reijngoud DJ, Groen AK, Kuipers F. Carbohydrate-response-element-binding protein (ChREBP) and not the liver X receptor α (LXRα) mediates elevated hepatic lipogenic gene expression in a mouse model of glycogen storage disease type 1. Biochem. J. 2010: 432: 249-254

	15. Oosterveer MH, **Grefhorst A**, Groen AK, Kuipers F. The liver X receptor: control of cellular lipid homeostasis and beyond. Implications for drug design. Prog. Lipid Res. 2010: 49: 343-352 16. Laskewitz AJ, van Dijk TH, Bloks VW, Reijngoud DJ, van Lierop MJ, Dokter WH, Kuipers F, Groen AK, **Grefhorst A**. Chronic prednisolone treatment reduces hepatic insulin sensitivity while perturbing the fed-to-fasting transition in mice. Endocrinology 2010: 151:2171-2178.