Erasmus University Rotterdam, the Netherlands
CSC PhD 2015 Project Description

School/Department:	Department of Internal Medicine, Erasmus MC, Rotterdam, The Netherlands. Laboratory of Reproduction and Metabolism PhD program is part of the post-graduate school Molecular Medicine (www.molmed.nl)
Project Title:	A gender-specific approach to identify novel targets for diabetes treatment and prevention
Abstract:	Type 2 diabetes (T2D), associated with obesity and insulin-resistance, is a major health problem of epidemic proportions. Women with polycystic ovary syndrome (PCOS), a disorder with a 10% prevalence and associated with infertility and metabolic disturbances, have a 5- to 7-fold increased risk of developing T2D compared to healthy women. In the general population, diabetic women have a higher risk of diabetic complications, such as cardiovascular disease, compared to diabetic men. Thus, gender-specific mechanisms are involved in the development of T2D and its complications, which implies a need for gender-specific therapeutic approaches. Using a mouse model with increased follicle growth, one of the hallmarks of PCOS, we observed that ovarian growth factors contribute to metabolic disturbances independently of sex steroids. These anti-Müllerian hormone (AMH)-deficient mice became glucose intolerant when fed a high fat diet (HFD), while insulin levels were not affected. In contrast, HFD-fed WT mice had a normal glucose tolerance in the presence of compensatory hyperinsulinemia. Since AMH has no known biological action beyond the reproductive system, the observed findings suggest that the altered profile of ovarian growth factors affects metabolism. This proposal is, therefore, aimed at understanding the role of ovarian growth factors in the development of insulin resistance and T2D. The objectives of this proposal are: firstly, to identify the ovarian growth factor(s) involved; and secondly, to unravel the mechanisms by which ovarian growth factors exert their metabolic action. Eventually, this will lead to the identification of novel risk markers and novel therapeutic targets for diabetes.
Requirements of candidate:	Master degree: Yes Background: Molecular Biology with knowledge of (Metabolic) Physiology IELTS Grade: 7.0 *(minimal 6.0 per component)* *or* TOEFL: *100 (minimal 20 per component)*

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Supervisor information:	Dr. ir. Jenny A. Visser j.visser@erasmusmc.nl http://www.erasmusmc.nl/inwendige_geneeskunde/endocrinologie/research/metabolisme **Selection of recent publications:** 1. Cousminer et al. Genome-wide association study of sexual maturation in males and females highlights a role for body mass and menarche loci in male puberty. Hum Mol Genet. 23(16):4452-4464, 2014. 2. Robertson et al. Detection of serum antimüllerian hormone in women approaching menopause using sensitive antimüllerian hormone enzyme-linked immunosorbent assays. Menopause 2014, in press 3. Wester et al. Long-term cortisol levels measured in scalp hair of obese patients. Obesity 2014, in press 4. Dewailly et al. The physiology and clinical utility of anti-Mullerian hormone in women. Hum Reprod Update. 20(3):370-385, 2014. 5. van Houten and Visser. Mouse models to study polycystic ovary syndrome: a possible link between metabolism and ovarian function? Reprod Biol, 14(1):32-43, 2014. 6. Ozcan et al. Does des-acyl ghrelin improve glycemic control in obese diabetic subjects by decreasing acylated ghrelin levels? Eur J Endocrinol. 170(6):799-807, 2014. 7. Dowman et al. Loss of 5α-Reductase Type 1 Accelerates the Development of Hepatic Steatosis but Protects Against Hepatocellular Carcinoma in Male Mice. Endocrinology 154(12): 4536-4547, 2013. 8. Labruijere et al. Analysis of the vascular responses in a murine model of polycystic ovary syndrome. *J Endocrinol* 218 (2): 205-213, 2013. 9. van Houten et al. Bone morphogenetic proteins and the polycystic ovary syndrome. J Ovarian Res. 2013 Apr 30;6(1):32. 10. van Dorp et al. Decreased ovarian function is associated with obesity in very long-term female survivors of childhood cancer. Eur J Endocrinol. 168(6):905-912, 2013. 11. Fernández-Rhodes et al. Association of Adiposity Genetic Variants With Menarche Timing in 92,105 Women of European

	Descent. Am J Epidemiol. 178(3):451-460, 2013. 12. Cousminer et al. Genome-wide Association and Longitudinal Analyses Reveal Genetic Loci Linking Pubertal Height Growth, Pubertal Timing, and Childhood Adiposity. Hum Mol Genet. 22(13):2735-2747, 2013. 13. Lie Fong et al. Serum anti-Müllerian hormone levels in healthy females: a nomogram ranging from infancy to adulthood. J Clin Endocrinol Metab 97(12):4650-4655, 2012. 14. van Houten et al. Reproductive and metabolic phenotype of a mouse model of PCOS. Endocrinology, 153:2861-2869, 2012. 15. Stolk et al. Meta-analyses identify 13 loci associated with age at menopause and highlights DNA repair and immune pathways. Nature Genetics, 44(3):260-268, 2012. 16. Visser et al. Anti-Müllerian hormone: an ovarian reserve marker in primary ovarian insufficiency. Nature Reviews Endocrinology, 8(6):331-341, 2012. 17. Kiewiet et al.Acute effects of acylated and unacylated ghrelin on total and high molecular weight adiponectin in morbidly obese subjects. J Endocrinol Invest. 34:434-438, 2011 18. Elks et al. Thirty new loci for age at menarche identified by a meta-analysis of genome-wide association studies. Nature Genetics 42(12):1077-1085, 2010 19. Delhanty et al. Unacylated ghrelin rapidly modulates lipogenic and insulin signaling pathway gene expression in metabolically active tissues of GHSR deleted mice. PLoS One, 5(7): e11749, 2010. 20. Perry et al. Loci on Chromosome 6 and 9 are associated with Age at Menarche: a Meta-analysis of Genome Wide Association Data from 17,510 Caucasian Women . Nature Genetics, 41:648-650, 2009. 21. Stolk et al. Loci at chromosome 13, 19 and 20 influencing age at natural menopause. Nature Genetics, 41:645-647, 2009. 22. Kevenaar et al. Polymorphisms in the ACVR1 gene are associated with AMH levels in women with Polycystic Ovary Syndrome. Human Reproduction, 24:241-249, 2009.