ERASMUS UNIVERSITEIT ROTTERDAM

Erasmus University Rotterdam, the Netherlands
CSC PhD 2015 Project Description

School/Department:	Erasmus University Medical Center Postgraduate School Molecular Medicine Department of Internal Medicine
Project Title:	**Molecular mechanisms of thyroid hormone resistance**
Abstract:	Thyroid hormone (TH) is essential for the development of many tissues, in particular the brain. This is illustrated by the severe consequences of untreated congenital hypothyroidism, resulting in growth failure and permanent mental retardation. Most actions of TH are exerted by binding of the active hormone T3 to nuclear receptors, leading to an altered expression of TH-responsive genes. TH action is thus determined by the proper expression of T3 receptors and by the intracellular T3 concentration. The latter is locally regulated by 1) activities of transporters mediating the cellular uptake and/or efflux of TH, and 2) activities of deiodinases catalyzing the activation or inactivation of TH. Over the last few years, our group has discovered two clinical syndromes of resistance to TH caused by mutations in the TH transporter MCT8 or in the T3 receptor TRα1 (1,2). MCT8 mutations cause severe psychomotor retardation, while TRα1 mutations result in variable defects in bone, brain, and intestinal development. An important part of the biochemical phenotype of TRa1 mutations involves an impaired regulation of the TH-degrading deiodinase D3. Induction of D3 is an important mechanism for lowering of T3 in pathological conditions (e.g. severe illness, carcinogenesis), and represents a novel mechanism of TH resistance. This project aims to determine the molecular mechanisms for the regulation of D3 in health and disease. In particular, we will investigate the reciprocal relationship between the regulation of tissue D3 expression and local TH availability. 1. Friesema, EC et al. Lancet 2004; 364: 1435-7 2. Van Mullem A et al. N Eng J Med 2012; 366: 1511-3
Requirements of candidate:	Master's degree in biomedical sciences, biochemistry or molecular biology. IELTS Grade: 7.0 *(minimal 6.0 per component)* *or* TOEFL: *100 (minimal 20 per component)*
Supervisor information:	Dr R.P. Peeters / Prof. dr. T.J. Visser Email address: r.peeters@erasmusmc.nl / t.j.visser@erasmusmc.nl www.erasmusmc.nl/schildkliercentrum

	Selected recent publications: 1) *Peeters RP, Wouters P, Kaptein E, et al. Reduced activation and increased inactivation of thyroid hormone in tissues of critically ill patients. J Clin Endocrinol Metab 2003; 88: 3202-11.* 2) *Friesema, ECH, Ganguly S, Abdalla A, et al. Identification of monocarboxylate transporter 8 as a specific thyroid hormone transporter. J Biol Chem 2003; 278: 40128-35.* 3) *Friesema ECH, Grueters A, Biebermann H, et al. Association between mutations in a thyroid hormone transporter and severe X-linked psychomotor. Lancet 2004; 364: 1435-7.* 4) *Peeters RP, Wouters PJ, van Toor H, et al. Serum rT3 and T3/rT3 are prognostic markers in critically ill patients and are associated with post-mortem tissue deiodinase activities. J Clin Endocrinol Metab 2005; 90: 4559-65.* 5) *Boelen A, Kwakkel J, Alkemade A, et al.Dramatic induction of type 3 deiodinase activity in inflammatory cells of mice with chronic local inflammation. Endocrinology 2005; 146: 5128-34.* 6) *Friesema ECH, Jansen J, Heuer H, et al. Mechanisms of disease: psychomotor retardation and high T3 levels caused by mutations in the monocarboxylate transporter 8. Nat Clin Pract Endocrinol Metab 2006; 2: 512-23.* 7) *Friesema ECH, Kuiper GGJM, Jansen J, et al. Thyroid hormone transport by the human monocarboxylate transporter 8 and its rate-limiting role in intracellular thyroid hormone metabolism. Mol Endocrinol 2006; 20: 2761-72.* 8) *Kester MHA, Kuiper GGJM, Versteeg R, Visser TJ. Regulation of type III iodothyronine deiodinase in human cell lines. Endocrinology 2006; 147: 5845-54.* 9) *Trajkovic M, Visser TJ, Mittag J, et al. Abnormal thyroid hormone metabolism in mice lacking the monocarboxylate transporter 8. J Clin Invest 2007; 117: 627-35.* 10) *Moreno JC, Klootwijk W, van Toor H, et al. Mutations in the iodotyrosine deiodinase gene and hypothyroidism. N Eng J Med 2008; 358: 1811-8.* 11) *Van der Deure WM, Hansen PS, Peeters RP, et al. Thyroid hormone transport and metabolism by OATP1C1 and consequences of genetic variation. Endocrinology 2008; 149: 5307-14.* 12) *Visser WE, Friesema ECH, Jansen J, Visser TJ. Thyroid hormone transport in and out of cells. Trends Endocrinol Metab 2008; 19: 50-6.* 13) *Kester MHA, Toussaint MJM, Punt CA, et al. Large induction of type III deiodinase expression after partial hepatectomy in the*

regenerating mouse and rat liver. Endocrinology 2009; 150: 540-5.

14) *Visser WE, Heemstra KA, Swagemakers SM, et al. Physiological thyroid hormone levels regulate numerous skeletal muscle transcripts. J Clin Endocrinol Metab 2009; 94: 3487-96.*
15) *Visser WE, Swagemakers SM, Ozgur Z, et al. Transcriptional profiling of fibroblasts from patients with mutations in MCT8 and comparative analysis with the human brain transcriptome. Hum Mol Genet 2010; 19: 4189-200.*
16) *Kappers MH, van Esch JH, Smedts FM, et al. Sunitinib-induced hypothyroidism Is due to induction of type 3 deiodinase activity and thyroidal capillary regression. J Clin Endocrinol Metab 2011; 96: 3087-94.*
17) *Medici M, de Rijke YB, Peeters RP, et al.Maternal early pregnancy and newborn thyroid hormone parameters: The Generation R Study. J Clin Endocrinol Metab 2012; 97: 646-52.*
18) *Van Mullem A, van Heerebeek R, Chrysis D, et al. Clinical phenotype and mutant TRα1. N Engl J Med 2012; 366: 1451-3.*
19) *Horn S, Kersseboom S, Mayerl S, et al.Tetrac can replace thyroid hormone during brain development in mouse mutants deficient in the thyroid hormone transporter Mct8. Endocrinology 2013; 154: 968-79.*
20) *Kersseboom S, Kremers GJ, Friesema EC, et al. Mutations in MCT8 in Patients with Allan-Herndon-Dudley-Syndrome Affecting Its Cellular Distribution. Mol Endocrinol 2013; 27: 801-13.*
21) *Van Mullem AA, Chrysis D, Eythimiadou A, et al.Clinical phenotype of a new type of thyroid hormone resistance caused by a mutation of the TRα1 receptor; consequences of LT4 treatment. J Clin Endocrinol Metab 2013; 98: 3029-38.*
22) *Medici M, Porcu E, Pistis G, et al. Identification of novel genetic Loci associated with thyroid peroxidase antibodies and clinical thyroid disease. PLoS Genet. 2014 Feb 27;10(2):e1004123.*
23) *Korevaar TI, Steegers EA, Schalekamp-Timmermans S, et al. Soluble Flt1 and Placental Growth Factor Are Novel Determinants of Newborn Thyroid (Dys)Function: the Generation R Study.J Clin Endocrinol Metab. 2014 Jun 2 [Epub ahead of print]*
24) *Zevenbergen C, Klootwijk W, Peeters RP, et al. Functional Analysis of Novel Genetic Variation in the Thyroid Hormone Activating Type 2 Deiodinase.J Clin Endocrinol Metab. 2014 Aug 20 [Epub ahead of print]*

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