ERASMUS UNIVERSITEIT ROTTERDAM

Erasmus University Rotterdam, the Netherlands
CSC PhD 2015 Project Description

School/Department:	Pediatric Surgery, Erasmus MC-Sophia Children's Hospital
Project Title:	The role of perivascular cells in the development of pulmonary hypertension
Abstract:	**Background:** Pulmonary vascular disease (PVD) embodies all congenital or acquired pathologies that affect the pulmonary vasculature, like pulmonary hypertension of the newborn (PPHN), characterized by a persistence of a high pulmonary vascular resistance (PVR) and abnormal vascular responsiveness. The pathology shows pulmonary vascular remodeling, including an expansion of vascular smooth muscle cells (VSMCs) in partially and non-muscularized peripheral arteries, which originate from perivascular cells (PVC). It is unknown what triggers this neo-muscularization, but previously we reported that VSMCs in PPHN lungs extend more distally than in controls, which support neo-muscularization and our preliminary data suggest that PVCs in a rat PPHN model prematurely differentiated. Previously, we have shown that the pulmonary vasculature is already a functional network at the onset of lung development, which expands as the lung grows through distal angiogenesis. So, we hypothesize that the initial population of pericytes at the onset of lung development is intrinsically different in PPHN, causing vascular remodeling ***Aims:*** The general aim of the project is to elucidate the central role of pericytes in the development of pulmonary vascular disease, and more specifically in pulmonary hypertension of the newborn. ***Study design and methods:*** In order to study the pericyte population in relation to PPHN, we will use a nitrofen induced rodent model. We will map the spatial and temporal distribution of PVCs in normal and abnormal lung development in relation to endothelial cells. Furthermore, we will isolate PVCs using Fluorescent Activated Cell Sorting (FACS) to perform transcriptome analysis, *in vitro* differentiation assays upon growth factor modulation and co-cultures with endothelial cells. Moreover, we will analyze the effect of nitrofen on the early mesenchymal pericyte population, and study the expression of signaling molecules, such as Fgf10 and Tgfß, in relation to the maturation of pericytes and to the branching of the airways. We will continuously extrapolate our findings to address whether pericytes are implicated in human pulmonary vascular disease. Therefore, human pathology samples from infants with PPHN will be compared to age matched controls. ***Clinical and/or scientific relevance:*** Congenital anatomical malformations form one of the largest research areas of the Erasmus MC – Sophia Children's Hospital. PPHN, either as primary disease or associated with lung-associated diseases is clinically characterized by a persistent high

	pulmonary vascular resistance after birth and is a critical determinant of morbidity and mortality. The concurrent vascular remodeling is not well understood, and focusing on the development of PVCs may help to better understand the process of neo-muscularization in PPHN. This may lead to new and/or targeted therapeutic strategies to improve the clinical outcome of affected infants. In addition, the results of our study may be extrapolated to other forms of pulmonary vascular disease, thus providing a basis for therapeutic pharmacological interventions and further research.
Requirements of candidate:	Master degree: Yes Background: The candidate should have a proficient background of (molecular) biology, able to handle laboratory animals and a team player IELTS Grade: 7.0 *(minimal 6.0 per component)* *or* TOEFL: *100 (minimal 20 per component)*
Supervisor information:	Dr Robbert J. Rottier e-mail: r.rottier@erasmusmc.nl website: http://www.erasmusmc.nl/cellbiology/research/research-groups/rottier/ recent publications: see Pubmed, search term “Rottier, R” Some important publications for this work: Etiological and pathogenic factors in congenital diaphragmatic hernia. Sluiter I, Veenma D, van Loenhout R, Rottier R, de Klein A, Keijzer R, Post M, Tibboel D. *Eur J Pediatr Surg. 2012 Oct;22(5):345-54.* Premature differentiation of vascular smooth muscle cells in human congenital diaphragmatic hernia. Sluiter I, van der Horst I, van der Voorn P, Boerema-de Munck A, Buscop-van Kempen M, de Krijger R, Tibboel D, Reiss I, Rottier RJ. *Exp Mol Pathol. 2013 Feb;94(1):195-202* Vascular abnormalities in human newborns with pulmonary hypertension. Sluiter I, Reiss I, Kraemer U, Krijger Rd, Tibboel D, Rottier RJ. *Expert Rev Respir Med. 2011 Apr;5(2):245-56.* Congenital lung lesions--underlying molecular mechanisms. Correia-Pinto J, Gonzaga S, Huang Y, Rottier R. *Semin Pediatr Surg. 2010 Aug;19(3):171-9.* Fetal lung and diaphragm development in congenital diaphragmatic hernia.

	Rottier R, Tibboel D. *Semin Perinatol. 2005 Apr;29(2):86-93.* Distal angiogenesis: a new concept for lung vascular morphogenesis. Parera MC, van Dooren M, van Kempen M, de Krijger R, Grosveld F, Tibboel D, Rottier R. *Am J Physiol Lung Cell Mol Physiol. 2005 Jan;288(1):L141-9*