

<b>School/Department:</b>	Pediatric Surgery, Erasmus MC-Sophia Children's Hospital
<b>Project Title:</b>	Strict regulation of Sox2 is essential for normal pulmonary development and repair
<b>Abstract:</b>	<p><b>Background:</b> Newborns and children with various congenital lung disorders are frequently treated at the Erasmus MC, but the underlying cause of their anomaly is mostly unknown. In addition, the continuous insults on the lung caused by artificial ventilation, requires a highly controlled mechanism of airway repair. Pathways that are active during development are re-activated upon damage. Our research focusses on the developmental aspects of the lung in relation to these anomalies. We have shown the importance of the transcription factor Sox2 in the formation of the bronchial tree, as well as the differentiation of the airway epithelium. Sox2 is expressed in a specific temporal and spatial pattern during lung development, but it is not known what regulates this specific expression pattern, nor is it known how Sox2 exerts its activity.</p> <p><b>Aims:</b> In order to unravel the expression pattern and different activities of Sox2, we will use a genetic, biochemical and cell biological approach to (1) identify genomic regions of the Sox2 gene that are important for its correct temporal and spatial regulation, to (2) subsequently identify the factors involved in this tight expression regulation, to (3) investigate the role of Sox2 in the generation of the different epithelial progenitor/stem cells, and (4) to address the role of Sox2+ cells in repair.</p> <p><b>Study design and methods:</b> The lung-specific enhancers of the Sox2 locus will be analyzed by transient transgenics, and transcription factors binding to these regions will be isolated and characterized further by expression analysis, ChIPs and transactivation studies. The role of Sox2 in airway differentiation will be elucidated by using various mouse strains, such as conditional Sox2 knockout mice and inducible Sox2 transgenics. In vitro cultures will be manipulated with chemical inhibitors or activators, and by gene specific expression modulation by siRNA technology and expression constructs. The role of Sox2 in repair will be investigated with the described mouse strains and inducible lung damage models, like naphtalene and SO<sub>2</sub>.</p> <p><b>Clinical and/or scientific relevance:</b> This research proposal will contribute to the general understanding of the molecular biology of the lung and to the understanding of the underlying causes of very complex congenital lung disorders.</p>

**Erasmus University Rotterdam, the Netherlands**  
**CSC PhD 2015 Project Description**

<b>Requirements of candidate:</b>	<p>Master degree: Yes</p> <p>Background: The candidate should have a proficient background of (molecular) biology, able to handle laboratory animals and a team player</p> <p>IELTS Grade: 7.0 (<i>minimal 6.0 per component</i>)  or  TOEFL: 100 (<i>minimal 20 per component</i>)</p>
<b>Supervisor information:</b>	<p>Dr Robbert J. Rottier  e-mail: <a href="mailto:r.rottier@erasmusmc.nl">r.rottier@erasmusmc.nl</a>  website: <a href="http://www.erasmusmc.nl/cellbiology/research/research-groups/rottier/">http://www.erasmusmc.nl/cellbiology/research/research-groups/rottier/</a>  recent publications: see Pubmed, search term "Rottier, R"  Some important publications for this work:</p> <p><u>Differentiated type II pneumocytes can be reprogrammed by ectopic Sox2 expression.</u> Ochieng JK, Schilders K, Kool H, Buscop-Van Kempen M, Boerema-De Munck A, Grosveld FG, Wijnen RM, Tibboel D, Rottier RJ. PLoS One, in press, 2014</p> <p><u>Sox2 regulates the emergence of lung Basal cells by directly activating the transcription of trp63.</u> Ochieng JK, Schilders K, Kool H, Boerema-De Munck A, Buscop-Van Kempen M, Gontan C, Smits R, Grosveld FG, Wijnen RM, Tibboel D, Rottier RJ. <i>Am J Respir Cell Mol Biol.</i> 2014 Aug;51(2):311-22</p> <p><u>Exportin 4 mediates a novel nuclear import pathway for Sox family transcription factors.</u> Gontan C, Güttler T, Engelen E, Demmers J, Fornerod M, Grosveld FG, Tibboel D, Görlich D, Poot RA, Rottier RJ. <i>J Cell Biol.</i> 2009 Apr 6;185(1):27-34.</p> <p><u>Sox2 is important for two crucial processes in lung development: branching morphogenesis and epithelial cell differentiation.</u> Gontan C, de Munck A, Vermeij M, Grosveld F, Tibboel D, Rottier R. <i>Dev Biol.</i> 2008 May 1;317(1):296-309</p>