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 use of patient-derived iPS cells to study the origin and development of congenital diaphragmatic hernia
Abstract:	**Background:** Congenital diaphragmatic hernia (CDH) is a developmental defect leading to structural defects of the diaphragm resulting in the presence of abdominal organs in the thoracic cavity. Moreover, this is accompanied by lung hypoplasia and debilitating pulmonary hypertension, which is the determining factor in the mortality and morbidity of the disease. Although whole genome association studies of CDH patients revealed several loci to be involved, mostly related to the retinoic acid pathway, no molecular explanation has yet been found to explain the pathogenesis. The lack of knowledge of the pathogenesis prevents the development of evidence-based and targeted therapeutic interventions of CDH. In part, this is due to the limited use of available fibroblasts and the absence of patient cells that lack lineage commitment. Recent developments to generate induced Pluripotent Stem cells (iPS), which may subsequently be triggered to develop into one of three germ layers, endoderm, mesoderm or ectoderm, will propel experiments that elucidate the role of a patient's genome in the interaction between germ layers, and may explain why specific genomic mutations may lead to CDH. **Aims:** We hypothesize that intrinsic cellular defects and the interaction between different cell types, is the basis of the development of CDH. However, the lack of useful human cells to study developmental stages at which the first defects arise, supports the search for alternatives such as the generation and use of multipotent iPS cells. Therefore, the aim of this proposal is (1) to implement the generation of iPS cells in our research using the expertise of the Erasmus Stem cell Institute (ESI), and (2) to investigate the differentiation potential of the established iPS cells to develop into lineages representing the three germ layers, such as endothelial and epithelial cells, and (3) to study the interaction between specific cell types. **Study design and methods:** High quality iPS cells will be generated from available fibroblast cell lines of human CDH patients. The quality of the iPS cells will be thoroughly checked with the help of the expertise of the ESI, and these cells will be used to investigate the molecular background of the pathogenesis of CDH. First, we will analyze if the CDH derived iPS cells have the potential to differentiate into cells of the three germ layers, endoderm, mesoderm and ectoderm. Secondly, to further study their developmental potential, we will setup different types of co-cultures with patient-derived and control cells, such as mixing endothelial cells and mesenchymal cells to study angiogenesis. Moreover, co-cultures with human lung explants or transplantation into decellularized lungs may complement the initial findings. **Clinical and/or scientific relevance:** The generation of patient derived iPS

	cells is important because it provides individualized stem cells of patients which are poorly accessible to obtain material from. It will accommodate and expand the GWAS studies performed previously, as well as provide tools to perform initial experiments to validate therapeutic agents. In addition, the multipotent nature of the iPS cells opens new pathways that will contribute to patient/disease oriented translational research to understand the molecular background of the developmental defects, the pathogenesis, drug testing and toxicity testing, all of which are nearly impossible in human studies. Clearly, establishment of iPS cells may lead to a strategy to perform cell-based therapy in congenital lung diseases, either as transplantable cells into a diseased lung, or to be grown on scaffolds that could replace diseased tissue in the lung.
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 and Dr Annelies de Klein 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: