

PhD Project Description

School/Department:	Department of Cell Biology, Erasmus MC
Supervisor information:	<ul style="list-style-type: none"> • Prof dr D. Huylebroeck, d.huylebroeck@erasmusmc.nl • Selected publications: Birkhoff et al. (2020) <i>Hum Mol Genet.</i> 29, 2535-2550. Vandamme et al. (2020) <i>Cancer Res.</i> 80, 2983-2995. Deryckere et al. (2020) <i>Development</i> 147, dev.184861. Dries R et al. (2020) <i>Stem Cells</i> 38:202-217. Dobrev MP*et al. (2018) <i>Development</i> 145, dev157222. Stryjewska A et al. (2017) <i>Stem Cells</i> 35:611-625. Wu LM et al (2016) <i>Nat Neurosci.</i> 19:1060-1072. Scott CL et al. (2016) <i>J Exp Med.</i> 213:897-911. Gomes Fernandes M et al. (2016) <i>J Exp Med.</i> 212, 2015-2025. Omlusik KD et al (2015) <i>J Exp Med.</i> 212, 2027-2039. van den Berghe V et al (2013) <i>Neuron</i> 77, 70-82.
Project Title:	Systems/Omics approaches to study nuclear interpretation of BMP signaling in stem/progenitor cells: ZEB2
Abstract:	<p>BMP signaling controls multiple cellular processes during embryogenesis and its developmental actions are recapitulated during tissue/organ repair. We address the multi-functional and multi-modal actions of the Mowat-Wilson Syndrome transcription factor ZEB2. Phenotypic analysis of conditional <i>Zeb2</i> KO mice, combined with biochemistry/omics has revealed multiple functions and mechanisms of action of the Smad-interacting protein Zeb2. Altogether, these models explain major aspects of Mowat-Wilson Syndrome (MOWS, OMIM#235730), including intellectual disability (brain cortex development), epilepsy (GABAergic interneurons in the ventral forebrain), Hirschsprung disease (neural crest, enteric nervous system) and other defects, including in neural crest derived craniofacial development. Additional mouse models reveal hitherto unknown and sometimes unexpected functions in e.g. myelination and (re)myelination, maturation of subtypes of immune cell, and Zeb2-mediated cardiac repair attempts in the infarcted heart. Our present work continues to study Zeb2 in neural differentiation of human and mouse ESCs, and human iPSCs from MOWS patients with new types of <i>ZEB2</i> mutation (including in the super enhancer gene desert of 3.3-3.7 Mb in length) and comparing the transcriptomes of the iPSCs under various differentiation protocols, also using cerebral organoids. We have identified Zeb2-dependent genes (RNA-Seq in <i>Zeb2</i>-KO cells) and novel protein partners (tag-Zeb2 proteomics), and are mapping Zeb2 genome-wide binding sites (ChIP-Seq) in neural as well as mesendodermal differentiation, and post-translational modifications affecting its stability. Importantly, novel insights in Zeb2 locus regulation itself by distant regulatory elements, which are likely relevant to MOWS as well, were obtained by using targeted chromatin conformation capture (T2C method). In addition to these studies, we would like to produce our own sets of genome-wide binding sites data for phospho-Smad1/5/9 binding in unstimulated and BMP/Nodal-stimulated ESCs, and compare these to Zeb2 binding sites, which will involve taking the cells into BMP/Nodal co-stimulated mesendodermal differentiation. Subsequent skeletal muscle differentiation is an option as well. Last, but not least, new projects are envisaged to study Zeb2 in various cancers, where together with its locus encoded lncRNA and its regulatory miRNAs it is studied intensively, by virtue of setting up tumor-immune cell (and other cell types) spheroids.</p>
Requirements of candidate:	<ul style="list-style-type: none"> • We are looking for highly motivated, talented students to join our international team. • Master degree or MD. • A fair scholarship that covers subsistence allowance and international air plane ticket. • Working in the lab requires that the student has good communication skills. • English language requirement: <i>English speaking countries & Netherlands:</i> no requirement <i>Other countries:</i> IELTS 7.0 (min 6.0 for all subs), TOEFL 100 (min 20 for all subs)

Application requirements & Deadlines:

<https://www.eur.nl/en/about-eur/erasmus-university-china-centre/csc-scholarship>

Erasmus MC, ranked world

* No.32 for Clinical Medicine US News 2020:

<https://www.usnews.com/education/best-global-universities/clinical-medicine?page=3>

* No. 30 Nature Index for Biomedical Sciences 2019:

<https://www.natureindex.com/supplements/nature-index-2019-biomedical-sciences/tables/healthcare>