Myogenic biomarkers in DM1 cell models

Myotonic dystrophy type I (DM1) is a heritable disorder that affects multiple organ systems. The genetic defect is present in a non-coding region of the gene and transcribed into an abnormally long mRNA. Secondary structure formation in this very long transcript leads to sequestration of RNA-binding proteins, which in turn leads to many of the observed symptoms in DM1.

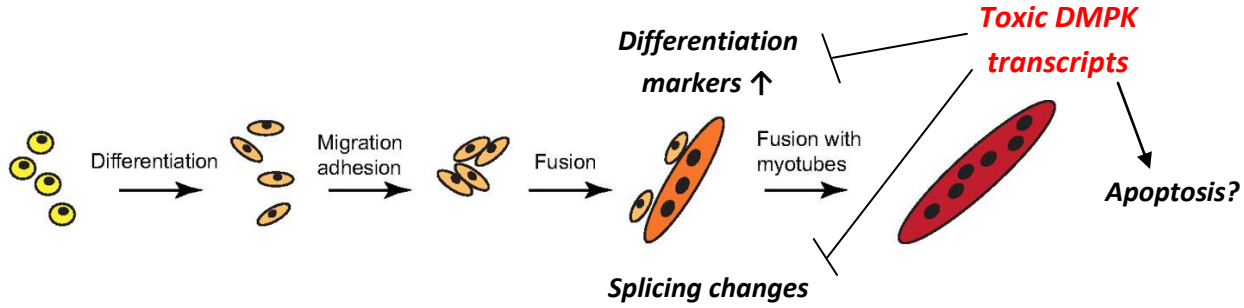
We are currently working on a strategy for a treatment of DM1 using antisense oligonucleotides (AONs) to block this so-called RNA gain-of-function mechanism (reviewed for example by Mulders et al. 2010).

Challenge

To determine the activity of therapeutic AONs *in vitro*, biomarkers that distinguish between the DM1 phenotype and a healthy phenotype are essential. Several reliable *in vitro* biomarkers are available for our myoblast cell models, but it is not yet clear how these biomarkers change during differentiation and to what extent they are affected by treatment with therapeutic AONs.

Internship project

Some of the biomarkers that are now used are DMPK mRNA expression, alternative splicing and cell fusion. How these biomarkers change during differentiation of myoblasts has not yet been investigated in-depth. Additionally, we would like to investigate the use of apoptosis as a possible biomarker. This is based on the finding of Loro et al. (2010), that differentiated DM1 myoblasts - which are then called myotubes - show more apoptosis than healthy myotubes.



It would be your task to determine how the different biomarkers change during differentiation and upon treatment with AONs. In addition, you would implement an apoptosis assay that can be used in our experiments. Different cell and molecular biological techniques will be involved, such as cell culture, fluorescence microscopy, RNA isolation, RT-PCR and RT-qPCR.

Has this project piqued your curiosity? Contact Leontien van der Bent, MSc (leontien.vanderbent@radboudumc.nl) or Dr. Rick Wansink (rick.wansink@radboudumc.nl) for more information and to discuss the possibilities.

Literature

Loro et al. 2010. "Normal Myogenesis and Increased Apoptosis in Myotonic Dystrophy Type-1 Muscle Cells." *Cell Death and Differentiation* 17 (8). Nature Publishing Group: 1315–24. doi:10.1038/cdd.2010.33.

Mulders et al. 2010. "Molecular Therapy in Myotonic Dystrophy: Focus on RNA Gain-of-Function." *Human Molecular Genetics* 19 (R1): R90–97. doi:10.1093/hmg/ddq161.