Molecular and Cellular Mechanisms in Myotonic Dystrophy and Strategies for Therapeutic Development

--- Internship possibilities (Note that we're booked up until Jan 2022) ---

SCIENTIFIC BACKGROUND

Myotonic dystrophy type 1 (*dystrophia myotonica*; DM1) is an autosomal dominant, multisystemic disorder, which can affect all age groups and involves many different organs, including skeletal muscle, heart and brain. At the basis of the disease is a (CTG)n trinucleotide repeat expansion mutation located in the 3' untranslated region of the *DMPK* gene and the promoter area of the *SIX5* gene (Fig. 1, left). Above a threshold of ~37 triplets the repeat becomes unstable between generations and during ageing in somatic cells. Hence, length of the (CTG)n repeat is highly variable. (CTG)n repeat length does correlate with severity and age of onset of the disease in patients.

How does a non-coding (CTG)n repeat cause the highly variable constellation of symptoms of DM1? Most of the current experimental evidence supports a toxic RNA gain-of-function model for *DMPK* RNA carrying a long expanded (CUG)n repeat. The (CUG)n segment aberrantly binds RNA-binding proteins like MBNL and CUGBP1 (Fig. 1, right), which in turn leads to dysregulation of splicing and transcription in cells where *DMPK* is expressed. In addition, we postulate that the (CUG)n RNA-protein aggregates also have wider implications on the cell's wellbeing and may be considered a continuous source of cell stress.

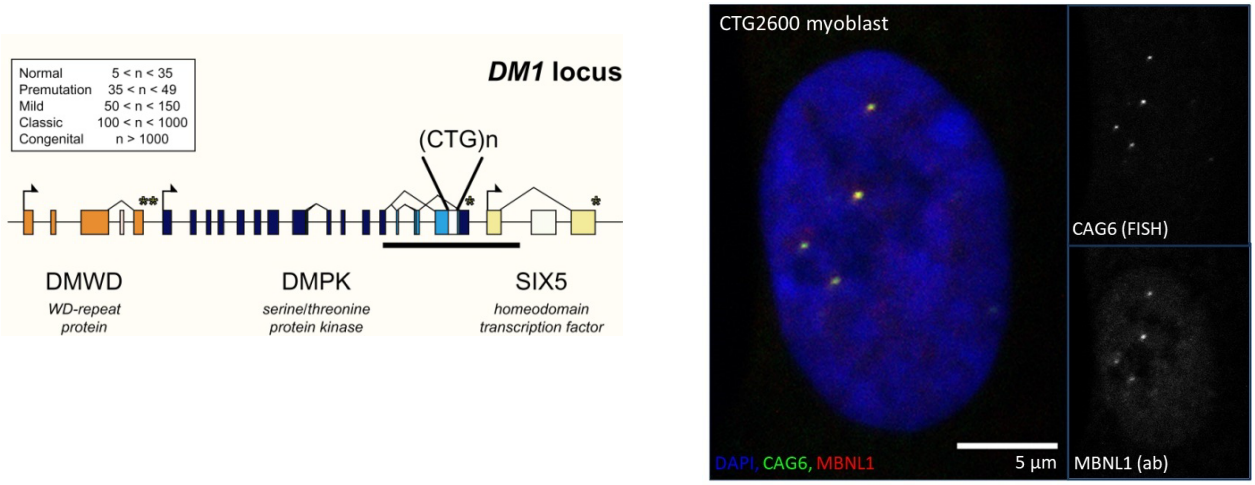

Figure 1. LEFT: A schematic representation of the DM1 locus and the relationship between repeat length and disease severity. RIGHT: Expanded (CUG)n repeat RNAs detected as nuclear foci, the hall mark of DM1.

CURRENT TOPICS

Our group has been studying the molecular pathogenesis of DM1 and the development of therapeutic strategies for more than 25 years now. Publications can be found here.

The following research topics and projects currently run in the DM group (May 2021):

(i) CRISPR/Cas-mediated gene editing as a therapeutic strategy and for the generation of cell models.
(ii) Therapeutic antisense oligonucleotides for DM1 (with Dept. of Biochemistry, Prof. Roland Brock)
(iii) Cell-based therapy using pericytes and iPSCs (with Dept. of Genetics, Prof. Hans van Bokhoven)
(iv) The development of 3D skeletal muscle organoids (with Dept. of Biomaterials, Dr Frank Walboomers)

In our research, we use various techniques ranging from biochemical, molecular biological, cell biological and genetic techniques to state-of the-art microscopy. Starting date of an internship depends on the availability of the intern, the supervisor and work space in the lab. In general, an interview is part of the selection process. The intern will be given a personal project to carry out, fitting within the general research theme of the group. The precise topic of a project will depend on ongoing research in the department and will be composed in close collaboration with the applicant, according to his/her research interests.

INTERESTED? CONTACT ME TO INQUIRE ABOUT THE POSSIBILITIES FOR THE MOMENT. **NOTE THAT WE'RE FULLY BOOKED UNTIL DEC 2021.**

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