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VRIJE UNIVERSITEIT BRUSSEL

PhD in Medical Sciences
2020-2021

INVITATION to the Public defence of

Silvie FRANCK

To obtain the academic degree of **'DOCTOR OF MEDICAL SCIENCES'**

The molecular basis of an expandable gene: focus on DM1

The defence will take place on **Tuesday, 2nd March 2021 at 5 p.m.**

and will be organised **online** accessible through the following link:

https://vub-qf.zoom.us/j/94020600796?pwd=bkFLdWpDSEpuelqwcmNsVmNPYWVZQT09

Meeting ID: 940 2060 0796
Password: 969925

Summary of the dissertation

The molecular basis driving the unstable character of repetitive sequences, eventually causing disease, is not well understood, but it is generally accepted that DNA metabolic processes are at the basis of this repeat instability which progresses pathogenesis. This thesis focusses on two such DNA metabolic processes which could contribute to the trinucleotide unstable character seen in DM1 and were investigated in *in vitro* cultured human embryonic stem cells and their derived myoblasts and myotubes.

The first aim was to assess the specific role of the mismatch repair component MSH2 on either CTG repeat instability and CpG methylation upstream of the CTG repeat. MSH2 knock-out both stabilized the repeat and erased CpG methylation, while re-introduction of MSH2 only increased repeat instability without re-establishing CpG methylation, suggesting a connection in only one direction. In this study we not only confirm previously published observations that MSH2 indeed drives repeat expansions, but also cautiously suggest that MSH2 might participate in methylation maintenance and that other repair mechanisms possibly contribute to inducing demethylation.

The second part of this thesis consists of investigating differences between DM1 and non-DM1 samples during early myogenesis. The most striking observation here was a bi-allelic hypermethylation pattern at early myogenic developmental stages, which was not described before.

Our findings are small steps in a still growing understanding of repeat instability drivers and indicate that the interaction between the different DNA metabolic processes acting on repeat instability is rather complex. In this thesis we demonstrated that a multifactorial network of cis-and trans-acting factors is involved in the DM1 pathology. The future may hold new insights concerning DM1 cell-specific deregulated processes since human embryonic stem cells make the very onset of differentiation accessible for study and might shed light on the initiation of the pathology in disease-relevant cell types.

Curriculum Vitae

In 2013 Silvie started her University study in Biology at the University Antwerp. She graduated in 2015 as Cell and System Biology. Thereafter she enrolled in a PhD program investigating the molecular basis of myotonic dystrophy type I, modelled in Embryonic stem cells.