Board of examiners

Dr. Rachel Eiges
Shaare Zedek Medical Center
The Hebrew University School of Medicine Jerusalem
Israel

Prof. Elfride De Baere
Department of Pediatrics and Medical Genetics
Ghent University, Belgium

Prof. Thierry VandenDriessche
Department of Gene Therapy and Regenerative Medicine
Vrije Universiteit Brussel, Belgium

Dr. Alexander Gheldof
Center of Medical Genetics
Universitair Ziekenhuis Brussel, Belgium

Prof. Hilde Van de Velde, Chair
Center of Reproductive Genetics
Universitair Ziekenhuis Brussel, Belgium

Prof. Karen Sermon, Promotor
Department of Reproductive Genetics
Vrije Universiteit Brussel, Belgium

VRIJE UNIVERSITEIT BRUSSEL

PhD in Medical Sciences
2016-2017

INVITATION to the Public defence of

Lise Barbé

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

Identification of the molecular key drivers in disease development in myotonic dystrophy type I.

Tuesday 28 March 2017
Auditorium **Piet Brouwer**, 18:00
Faculty of Medicine and Pharmacy, Laarbeeklaan 103, 1090 Brussel

How to reach the campus Jette:
http://www.vub.ac.be/english/infoabout/campuses

Summary of the dissertation

Myotonic dystrophy type I is the most common muscular dytrophy and is caused by an unstable trinucleotide 'CTG' repeat. Due to incomplete understanding of the repeat behaviour, the disease remains incurable. With this thesis, I further characterized two main molecular aspects of the disease being DNA methylation and its role in inheritance of the most severe forms of the disease and the influence of mismatch repair on repeat instability.

The disease has different clinical manifestations of which the congenital form is the most severe with large expansions and almost exclusive maternal transmission. The molecular factor determining the difference between the congenital and classical form is unknown. We correlated methylation in regions flanking the CTG repeat to the most severe forms of the disease. Almost all congenital patients showed methylation at both sides of the repeat which is in contrast with no methylation in classical patients except for the most severe forms. This highlights methylation as a potential prenatal indicator of the most severe forms of the disease, including the congenital form, which may guide families faced with an affected pregnancy.

The mismatch repair machinery and especially its component *MSH2* has been linked to repeat instability due to an incorrect repair creating repeat expansions. Incomplete understanding of this process is mainly due to the predominant use of mouse models that do not represent all DM1-related symptoms. This report is the first to study the role of MSH2 in DM1-affected human pluripotent stem cells, using a *MSH2* knock-out model by CRISPR/Cas9 technology. If the knock out of *MSH2* creates repeat stability or contractions as seen in mouse models, MSH2 could be used as a drug target to delay disease onset and slow down disease progression.

Curriculum Vitae

Barbé L, Stella Lanni, Arturo López-Castel, Silvie Franck, Claudia Spits, Kathelijn Keymolen, Sara Seneca, Stephanie Tomé, Ioana Miron, Julie Letourneau, Minggao Liang, Sanaa Choufani, Rosanna Weksberg, Michael D. Wilson, Zdenek Sedlacek, Cynthia Gagnon, Zuzana Musova, David Chitayat, Patrick Shanon, Jean Mathieu, Karen Sermon, Christopher E. Pearson. CpG methylation, a parent-of-origin effect for maternal biased transmission of congenital myotonic dystrophy. American Journal of Human Genetics (2017).

Dziedzicka D, Markouli C, **Barbé L**, Spits C, Sermon K, Geens M. A high proliferation rate is critical for reproducible and standardized embryoid body formation from laminin-521-based human pluripotent stem cell cultures. Stem Cell Reports and Reviews (2016).

Geens M, Seriola A, **Barbé L**, Santalo J, Veiga A, Dée K, Van Haute L, Sermon K, Spits C. Female human pluripotent stem cells rapidly lose X chromosome inactivation marks and progress to a skewed methylation pattern during culture. Mol Hum Reprod (2016).

Jacobs K, Zambelli F, Mertzanidou A, Smolders I, Geens M, Nguyen HT, **Barbé L**, Sermon K, Spits C. High density culture in human embryonic stem cells results in DNA damage and genomic instability. Stem Cell Reports (2016).

Nguyen HT, Markouli C, Geens M, **Barbé L**, Sermon K, Spits C. Human embryonic stem cells show low-grade microsatellite instability. Mol Hum Reprod. (2014); 20(10):981-989.