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Geneeskunde & Farmacie

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PhD in Medical Sciences
2015-2016

INVITATION to the Public defence of

Anna SERIOLA PETIT

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

Pluripotent stem cells as research models: the examples of trinucleotide repeat instability and X-chromosome inactivation

Monday 21 September 2015
Auditorium **Vanden Driessche**, 17:00
Faculty of Medicine and Pharmacy, Laarbeeklaan 103, 1090 Brussel

How to reach the campus Jette:
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Summary of the dissertation

Disease modelling is essential in biomedical research. In the past decade, human pluripotent stem cells (hPSC) emerged as an interesting option in the field of cellular modelling, this development in recent years having taken up much momentum.
In this work, we first aimed at characterizing hPSC as models for the study of Myotonic dystrophy type 1 (DM1) and Huntington's disease (HD) -associated trinucleotide repeat (TNR) instability. We show that the expanded CTG/CAG tract is highly unstable in DM1- but not HD-derived hPSCs. Upon differentiation, we find that the DM1 repeat looses instability, and this process occurs at the same time as a loss of expression of the mismatch repair machinery. This work is the first demonstration of the correlation between a biologically natural down-regulation of the mismatch repair proteins and changes in the stability of an endogenous disease locus.
In the second part of this thesis, we investigate the status of the X-chromosome inactivation in hPSC, and its evolution during in vitro culture, with an eye on using these cells as models for early human development. We show that hPSC rapidly lose X chromosome inactivation-linked marks during culture and progress to predominantly skewed DNA methylation patterns. These aberrations were not related to the parent of origin, were not passenger mutations, and were stably inherited by the differentiated progeny. Overall, hPSC appeared to good in vitro models for the study of DM1 and HD TNR instability, as the in vitro model follows the same patterns as found in vivo. Conversely, our results on the study of the X chromosome inactivation suggest that hPSC are not a good proxy to early embryonic cells, at least what XCI is concerned.

Curriculum Vitae

Anna Seriola Petit studied Biology at the Universitat Autonoma de Barcelona (Spain) and graduated in 2006. After, she did an internship at the Weill Medical College of Cornell University (New York) were she worked at the Embryology lab under Dr. Gianpiero Palermo's supervision. In November 2007, she joined the Research Group Reproduction and Genetics as a stem cell laboratory technician and to work for the European Union FP7 programme supported StemHD Project, on the study of the trinucleotide repeat instability in human embryonic stem cells. In 2008, she started a PhD with the Universitat Autonoma de Barcelona and the Vrije Universiteit Brussel, focused on genetic and epigenetic instability of hESC and its impact on the translation to clinic. Once she moved back to Spain in 2012, she worked for 1 year in the private sector at the pharmaceutical company Grifols as a publications assistant in the scientific department. From 2013 until recently, she worked as research assistant at the Center for Regenerative Medicine of Barcelona (CMRB, Spain) carrying out tasks for the European Human Pluripotent stem cell registry as well as doing research on human pluripotent stem cell differentiation into retinal pigmented epithelium and photoreceptors. During this same period, she completed the work presented in her PhD dissertation.