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PhD in Medical Sciences
2019-2020

INVITATION to the Public defence of

Christina MARKOULI

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

Losing Pluripotency. The impact of genomic alterations on differentiation.

Wednesday, 13 November 2019 at 5 p.m.

In Auditorium **Vanden Driessche**

Faculty of Medicine and Pharmacy, Laarbeeklaan 103, 1090 Brussels

How to reach the campus Jette:

<http://www.vub.ac.be/english/infoabout/campuses>

Summary of the dissertation

Since human pluripotent stem cells are currently making their way to the clinic, more and more studies are focusing on their safety. Within this scope, the field of genomic (in)stability has become widely explored and it is now known that pluripotent cells undergo recurrent changes in culture. While these alterations have been extensively reported, still a lot remains to be researched in terms of their driving mechanism and most importantly in regard to their impact upon differentiation.

In this thesis, we, for the first time, describe a clear effect upon TGF- β mediated neuroectoderm commitment of lines carrying a 20q11.21 amplification. This aberration is the most commonly found in human pluripotent cells, according to a worldwide study of 136 lines. All four mutant lines showed a transcriptomically unique profile, mainly influenced by the overexpression of *Bcl-xL*; the anti-apoptotic driver gene of the amplification. Despite their reduced efficiency for neuroectoderm formation, the mutant lines differentiated equally well as their normal counterparts towards mesendoderm.

Additionally, as part of the above study, we identified a subline with a 20q11.21 amplification that behaved abnormally upon mesendoderm induction. Transcriptomic analysis of the subline showed intrinsic deregulation of BMP4 and WNT pathways that promoted differentiation towards a trophoblast-like fate under common mesendoderm stimuli. The constitutional pathway activation could not be linked to any change in the genome, letting us speculate on a possible epigenetic cause.

Our findings are very the first steps towards a broader understanding of the effect of genomic changes upon differentiation. This topic plays a critical role in the selection process of appropriate material for clinical therapy.

Curriculum Vitae

Born in Athens, Greece, Christina completed her Bachelor studies in the Aristotle University of Thessaloniki with a major in Molecular Biology and Genetics. Her curiosity to explore life abroad influenced her next steps and brought her to Brussels where she joined the Vrije Universiteit Brussel for a MSc in Biology, specialised in Genetics, Cell and Developmental Biology. During her master thesis she joined the laboratory of Reproduction & Genetics where she later pursued her PhD researching the effect of recurrent genomic abnormalities upon the differentiation of human embryonic stem cells.