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VUB VRIJE UNIVERSITEIT BRUSSEL

UNIVERSITÁ DEGLI STUDI DI TERAMO

Joint PhD VUB & UniTe
2017-2018

INVITATION to the Public defence of

Filippo ZAMBELLI

To obtain the academic degree of

'DOCTOR IN MEDICAL SCIENCES'
'DOCTOR IN MOLECULAR AND CELLULAR BIOTECHNOLOGY'

Mitochondrial DNA variants in human pluripotent stem cells.

Thursday 29 March 2018
Auditorium **Vanden Driessche**, 16:00
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

Mitochondrial genetics is a rapidly expanding field due to the recent development of massive parallel sequencing, which has allowed overcoming several limitations historically associated to the study of the mitochondrial DNA (mtDNA). The technological advancements went along with a growing body of evidence associating mitochondrial function to the regulation of a wide variety of cellular processes, including embryonic development and pluripotency and differentiation of human pluripotent stem cells (hPSC).

The goal of our study was to analyse the variants in the mtDNA of hPSC, establishing their origin and evaluating the effects of prolonged in vitro culture. For this, we initially developed a method for an accurate analysis of both single nucleotide variants and large deletions in the mtDNA applicable also to single cells.

The method proved to be more accurate and sensitive than available softwares, and suitable for the identification of multiple deletions within the same sample, in both bulk DNA and single cells.

The study of the mtDNA of human embryonic stem cells showed few variants at low frequency in the early passages, and an increased presence of variants after prolonged in vitro culture. We identified the cause of the increased mutation load as a combination of high-grade mtDNA mosaicism and clonal culture takeover from a single cell, with the mtDNA variants being passenger mutations. Spontaneous mutagenesis doesn't seem to affect significantly the mtDNA variant load during in vitro culture. High-grade tissue mosaicism affects also the derivation of induced Pluripotent Stem Cells, generating lines with higher loads of variants as compared to their embryonic counterpart. Our work might be useful to develop guidelines for the genetic screening of human PSCs in clinical applications.

Curriculum Vitae

Filippo Zambelli attended the University of Bologna and received a bachelor degree in Biotechnology in 2007, with a thesis related to the development and mapping of functional markers in the invertase gene family in apple. In 2010 he received a Master degree in industrial and molecular biotechnology from the same University, with a thesis on the comparison of the differentiation potential of human and mouse embryonic stem cells. This project was a collaboration between the Sant' Orsola University Hospital in Bologna, and SISMeR, a private IVF clinic. In 2012 he obtained a PhD scholarship from The University of Teramo funded by SISMeR Bologna and in 2014 started a joint PhD between the University of Teramo and the Vrije Universiteit Brussels, under the supervision of prof. Claudia Spits. The main focus of this thesis is the analysis of mtDNA variants trough Massive Parallel Sequencing in human Pluripotent Stem Cells. During this period, he also performed the activity of Clinical Trial Monitor for the ESTEEM trial, for the Clinical Trial Center Maastricht. From 2013 to 2015 he has been the Junior Deputy of the Special Interest Group stem cells of the European Society of Human Reproduction and Embryology (ESHRE). Since 2017 he is the Junior Deputy of the special Interest group Reproductive Genetics of ESHRE.