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PhD in Medical Sciences
2016-2017

INVITATION to the Public defence of

Zhuo REN

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

The interrelationship between Nucleophosmin and STAT3/5 in cancer.

Monday 12 December 2016

Auditorium **P. Brouwer**, 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

The development and progression of cancer require the concerted activation and participation of a pool of different oncogenic signal pathways. Some of these oncogenic pathways converge at a nuclear phosphoprotein named nucleophosmin (NPM). NPM transcriptionally regulates p53 gene, and stabilizes its expression. It is also an important ubiquitination target of BRCA1-BARD1 complex, where cancer predisposing mutations occur leading to development of hereditary breast cancer. Moreover, genetic mutations on NPM gene were found to be associated with haematological malignancies including acute myeloid leukemia (AML) and anaplastic large T cell lymphoma (ALCL). In the development of ALCL, fusion protein NPM-ALK drives transformation of CD4+ T cells by phosphorylating members of signal transducer and activator of transcription (STAT) family. However, little is known how wild type NPM interacts with the signal pathways mentioned above in cancers.

The present thesis dissected this fundamental question into three more specific questions : (1) whether wild type NPM is functionally related to STAT3 in cancers; (2) whether there is a potentially regulatory relationship between NPM and STAT5 in cancers; (3) whether there is any cancer predisposing mutation in NPM gene in breast cancers bearing no BRCA1/2 mutation.

The first section of the thesis demonstrated that tyrosine 705 phosphorylated STAT3 (P-STAT3) physically interacts with NPM, and transcriptionally regulates the expression level of NPM gene. The second section further explored the relationship between STAT5 and NPM in cancers, and unveiled that phosphorylated STAT5 regulates p53 expression via BRCA1/BRAD1-NPM1 and MDM2 in cancers. The third section identified a genetic variation, c.772-46 C>A, among 198 high risk breast cancer families in which BRCA1/2 mutation was found negative. Though this mutation is not cancer predisposing, its *in vitro* expression accelerate the turnover of NPM protein, leading to its destabilization.

Curriculum Vitae

Postdoctoral training	Sep 2015 – Present
Princess Margaret Cancer Centre, University Health Network (UHN), Toronto	
Ph.D. studies	Oct 2007 - Dec 2016
Vrije Universiteit Brussel (VUB, Free University of Brussels), Brussels, Belgium	
M.Sc. studies in Surgical Oncology	Sep 2004 - Jul 2007
Shanghai Jiaotong University, Shanghai, China	
Medical doctoral studies	Sep 1999- Jul 2004
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