2016-03

IC-**3i** International PhD Program

PhD thesis project

2017 Call for application

Regulation of the WNT Signaling Pathway by Protein Arginine Methyltransferases in Triple-Negative Breast Cancers: From Basic to Translational Research

General information

Call	2017
Reference	2016-03-DUBOIS
Keyword(s)	breast cancer, protein arginine methyltransferases, WNT pathway, therapeutic target, drug resistance

Director(s) and team

Thesis director(s)	Thierry Dubois
Research team	Breast Cancer Biology
Research department	Translational Research

Description of the PhD thesis project

Although patients with triple-negative breast cancer (TNBC) respond well to conventional chemotherapies, they still represent a large proportion of breast cancer deaths due to a high recurrence rate of residual, resistant tumor cells. New treatments are therefore needed to bypass resistance to chemotherapies and to improve their survival rate.

The WNT pathway is activated in TNBC and specifically in breast cancer stem cells or tumor initiating cells which are enriched in this breast cancer subtype. These cells are suspected to be resistant to chemotherapy and hence responsible for relapses.

Protein arginine methylation, catalyzed by protein arginine methyltransferases (PRMTs), is a post-translational modification that regulates signaling pathways. We found that few PRMTs are overexpressed in TNBC and that their invalidation induces cell death, suggesting that these enzymes are attractive therapeutic targets. Few reports and our unpublished work indicate that some PRMTs regulate the WNT pathway.

The aim of the PhD project is to characterize the regulation of the WNT pathway by PRMTs in TNBC. The 1st objective will be to determine which PRMTs (PRMT1-9) regulate (positively or negatively) the WNT pathway in TNBC cell lines. We will then focus on the PRMTs that are overexpressed in TNBC and which activate the WNT pathway (our preliminary data indicate that this is the case for PRMT1). The 2nd objective will be to characterize the molecular mechanisms leading to WNT regulation. The 3rd objective will be to examine whether PRMT1 (potentially other PRMTs) invalidation affects, through WNT inhibition, the population of breast cancer stem cells or tumor initiating cells (in vitro) or the residual population in vivo (TNBC PDX models). The 4th objective will

be to explore the potential benefit of co-targeting PRMT1 (potentially other PRMTs) and the WNT pathway, both in vitro (TNBC cell lines) and in vivo (TNBC PDX models).

International, interdisciplinary & intersectoral aspects of the project

International:
The PhD project combines basic and translational research. The selected fellow will be mentored by Dr Jocelyn Côté (University of Ottawa, Faculty of Medicine, Department of Cellular and Molecular Medicine, Canada), who is internationally recognized as an expert in the field of PRMTs, more specifically PRMT1.

Intersectoral:
The project will also benefit from the expertise of an industrial mentor, Dr Francisco Cruzalegui (Director of Precision Medicine Oncology at Pierre Fabre Research Institute, France) who is an expert of the WNT signaling pathway.

Interdisciplinary:
The thesis project involves different domains: biochemistry/cell biology (in vitro) and preclinical research (patient-derived xenograft models).

Recent publications

1. Michaut M, Chin S-F, Majewski I, Severson T, Bismeijer T, de Koning L, Peeters J, Schouten P, Rueda O, Bosma A, Tarrant F, Fan Y, He B, Xu Z, Mittempergher L, Kluin R, Heijmans J, Snel M, Pereira B, Schlicker A, Provenzano E, Ali HR, Gaber A, Kay E, O'Hurley G, Wesseling J, Muris J, Lehn S, Sammut SJ, Bardwell H, Barbet A, Bard F, Lecerf C, O'Connor D, Vis D, Benes C, McDermott U, Garnett M, Simon I, Jirström K, **Dubois T**, Linn S, Gallagher W, Wessels L, Caldas C, Bernards R.
Integration of genomic, transcriptomic and proteomic data identifies two biologically distinct subtypes of invasive lobular breast cancer.
Sci Rep. 2016 Jan 5;6:18517. doi: 10.1038/srep18517.

2. Maubant S, Tesson B, Maire V, Ye M, Rigaill G, Gentien D, Cruzalegui F, Tucker GC, Roman-Roman S, **Dubois T**.
Transcriptome analysis of Wnt3a-treated triple-negative breast cancer cells.
PLoS One. 2015 Apr 7;10(4):e0122333. doi: 10.1371/journal.pone.0122333.

3. Baldeyron C, Brisson A, Tesson B, Némati F, Koundrioukoff S, Saliba E, De Koning L, Ye M, Rigaill G, Gentien D, Decaudin D, Debatisse M, Depil S, Cruzalegui F, Pierré A, Roman-Roman S, Tucker GC, **Dubois T**.
TIPIN depletion leads to apoptosis in breast cancer cells.
Mol Oncol. 2015 Oct;9(8):1580-98. doi: 10.1016/j.molonc.2015.04.010.

4. Maire V, Baldeyron C, Richardson M, Tesson B, Vincent-Salomon A, Gravier E., Marty-Prouvost B, De Koning L, Rigaill G, Dumont A, Gentien D, Barillot E, Roman-Roman S, Depil S, Cruzalegui F, Pierré A, Tucker GC, **Dubois T**.
TTK/hMPS1 is an attractive therapeutic target for triple-negative breast cancer.
PLoS One. 2013 May 20;8(5):e63712. doi: 10.1371/journal.pone.0063712.

5. Maire V, Némati F, Richardson M, Vincent-Salomon A, Tesson B, Rigaill G, Gravier E, Marty-Prouvost B, de Koning L, Lang G, Gentien D, Dumont A, Barillot E, Marangoni E, Decaudin D, Roman-Roman S, Pierré A, Cruzalegui F, Depil S, Tucker GC, **Dubois T.**
Polo-like kinase 1: a potential therapeutic option in combination with conventional chemotherapy for the management of patients with triple-negative breast cancer.
Cancer Res. 2013 Jan 15;73(2):813-23. doi: 10.1158/0008-5472.CAN-12-2633.

Expected profile of the candidate

We are looking for a highly enthusiastic and motived candidate, interested in the field of translational research. Knowledge in cancer biology and signaling pathways is strongly recommended. Experience in cell culture and biochemistry will be an advantage. Applicant must be fluent in English and must have excellent verbal and written communication skills. He/she must be strongly inclined to learn, very resourceful, and must have a creative approach to problem-solving. The candidate will develop his/her ability to work independently and will have to show initiative.