

EuReCa International PhD Program

PhD thesis project

2021 Call for application

Characterization of the functions of protein arginine methyltransferase 4 (PRMT4/CARM1) in triple-negative breast cancers

General information

Call	2021
Reference	2021-05-DUBOIS
Keyword(s)	PRMT4; CARM1; Breast Cancer; protein-protein interactions; arginine methylation

Director(s) and team

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

Description of the PhD thesis project

The poor prognosis-associated triple-negative breast cancer (TNBC) remains a major challenge for oncologists. A better understanding of the biology of TNBC could lead to new therapeutic strategies.

We have found that some protein arginine methyltransferases (PRMTs), which catalyze the methylation of arginine residues within proteins, are more expressed in TNBC compared to normal breast tissues, thus representing potential therapeutic targets.

PRMT4, better known as CARM1 is overexpressed in various tumors compared to normal tissues, and a hotspot mutation in CARM1 supports it as a cancer driver gene. Specific CARM1 inhibitors display anti-tumor activity in hematopoietic cancers. Among the different breast cancer types, CARM1 has been extensively studied in luminal breast cancer due to its role in activating estrogen receptor signaling pathway. Very little is known about the role of CARM1 in TNBC apart from promoting cell migration.

Two CARM1 variants are expressed in breast cancers: a full-length form (CARM1-FL) and a shorter spliced isoform (CARM1-ΔE15). CARM1-ΔE15 has been proposed to be the oncogenic form of CARM1, and is the most abundant form of CARM1 (about 80%) in breast cancers. However, only very few studies have explored the functions of CARM1-ΔE15 in cells. Indeed, CARM1-ΔE15 has not been taken into account in most CARM1 studies. So far, only one substrate has been reported to be methylated specifically by CARM1-ΔE15, and not by CARM1-FL, showing that both CARM1 forms can have specific functions. Concordantly, a recent study performed in our laboratory identified potential specific protein partners for CARM1-ΔE15.

The PhD program aims to decipher the specific functions of CARM1-ΔE15, the main CARM1 isoform expressed in breast cancers, by searching for specific partners/substrates of both CARM1-ΔE15 and CARM1-FL. The candidate will focus on few of them for further analyses, in particular by studying the impact of methylation on their functions.

International, interdisciplinary & intersectoral aspects of the project

The thesis program combines basic and translational research. It will benefit of an international mentor (Canada) who is internationally recognized as an expert on the field of PRMTs.

The project will also benefit of an industrial mentor who is an expert of translational research and cell signalling.

The research project involves different domains: biochemistry, cell biology, RNA metabolism, tumor biology.

Recent publications

Meseure D, Vacher S, Boudjemaa S, Marick L, Nicolas A, Leclerc R, Chemlali W, Champenois G, Schnitzler A, Lesage L, **Dubois T**, Bieche I (2020) Biopathological significance of PIWI-PiRNA pathway deregulation in invasive breast carcinomas. *Cancers*, 12, 2833

Zajac O, Leclerc R, Nicolas A, Meseure D, Marchiò C, Vincent-Salomon A, Roman-Roman S, Schoumacher M, **Dubois T** (2020) AXL controls directed migration of mesenchymal triple-negative breast cancer cells. *Cells* 9, pii: E247

Maire V, Mahmood F, Rigai G, Ye M, Brisson A, Némati F, Gentien D, Tucker GC, Roman-Roman S, **Dubois T** (2019) LRP8 is overexpressed in estrogen-negative breast cancers and a potential target for these tumors. *Cancer Medicine* 8, 325-336

Vinet M, Suresh S, Maire V, Monchecourt C, Némati F, Lesage L, Pierre F, Ye M, Lescure A, Brisson A, Meseure D, Nicolas A, Rigai G, Marangoni E, Del Nery E, Roman-Roman S, **Dubois T** (2019) Protein Arginine Methyltransferase 5: a novel therapeutic target for triple-negative breast cancers. *Cancer Medicine* 8, 2414-2428

Maubant S, Tahtouh T, Brisson A, Maire V, Némati F, Tesson B, Ye M, Rigai G, Noizet M, Dumont A, Gentien D, Marty-Prouvost B, de Koning L, Mahmood SF, Decaudin D, Cruzalegui F, Tucker GC, Roman-Roman S, **Dubois T** (2018) LRP5 regulates the expression of STK40, a new potential target in triple-negative breast cancers. *Oncotarget*, 9, 22586-22604

Expected profile of the candidate

We are looking for a highly enthusiastic and motivated candidate, interested in basic and translational research. Knowledge in cancer biology and signaling pathways is strongly recommended. Experience in cell culture and biochemistry will be an advantage.

Applicants 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 must have the capacity to work independently and to take initiative.