

GRAL PhD PROJECT 2020-2023

Title of the PhD project: Endothelial cell reprogramming in cancer microenvironment: Towards the identification of new therapeutic targets

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Summary of the project: This project aims at understanding the consequences of VE-cadherin modifications on Endothelial Cells functions in cancer. In the laboratory we have produced a new Y685F-VE-cadherin knock-in mouse (KI) in which all VEcadherin molecules are mutated on the tyrosine 685 (replaced by the non phosphorylable amino acid phenylalanine). Mutated ECs will be isolated from this mouse model, then analysed for their morphology, and functions. EC will be grown to perform several types of assays such as Cell culture wound closure assay, EC co-culture spheroids, the real-time random migration assay to measure migration and 3D models of vascular morphogenesis. The expressional effect of the mutation at site Y685 of VE-cadherin will be analysed by RNAseq to examine the transcriptome of purified ECs from Wild type and KI. The gene expression data generated by RNA-seq will be analyzed using Gene Set Enrichment Analysis to extract biological knowledge with critical keywords for the gene-sets such as clotting, inflammation, mitosis, fibrosis as they are linked with EC functions. Based on the results of the gene expression, the physiopathological analysis of specific organs of the KI mouse model will be performed. The new activated gene panel might identify new EC functions in the tumor context that can represent new potential targets in therapeutics.

Keywords: endothelial cell functions, tyrosine kinases, phosphorylations, gene expression, VE-cadherin

Applicant profile: Candidates should have a strong background in physiology, cell signalling, and biochemistry. Preliminary experience in mouse models will be a key advantage.

Three recent publications of the PhD supervisor

Polena H, Creuzet J, Dufies M, Sidibé A, Khalil-Mgharbel A, Salomon A, Deroux A, Quesada JL, Roelants C, Filhol O, Cochet C, Blanc E, Ferlay-Segura C, Borchiellini D, Ferrero JM, Escudier B, Négrier S, Pages G, Vilgrain I. The tyrosinekinase inhibitor sunitinib targets vascular endothelial (VE)-cadherin: a marker of response to antitumoural treatment in metastatic renal cell carcinoma. *Br J Cancer*. 2018 May;118(9):1179-1188.

Khalil-Mgharbel A, Polena H, Dembélé PK, Hasan Sohag MM, Alcaraz JP, Martin DK, Vilgrain I. A Biomimetic Lipid Membrane Device Reveals the Interaction of Cancer Biomarkers with Human Serum Lipidic Moieties. *Biotechnol J*. 2018 Dec;13(12):e1800463.

Rocheffort P, Chabaud S, Pierga JY, Tredan O, Brain E, Bidard FC, Schiffler C, Polena H, Khalil-Mgharbel A, Vilgrain I, Bachelot T. Soluble VE-cadherin in metastatic breast cancer: an independent prognostic factor for both progression-free survival and overall survival. *Br J Cancer*. 2017;116(3):356-361.