



## PHD STUDENT IN THE LABORATORY OF CONNECTIVE TISSUES BIOLOGY

The Giga Research Center is a multidisciplinary research group at the University of Liège aiming at developing applied genomics and proteomics research programs.

**Three PhD student positions** are available in the Laboratory of Connective Tissues Biology (LCTB). The LCTB is part of the GIGA –Cancer ([www.giga.uliege.be](http://www.giga.uliege.be)) which favors multiple interactions with other laboratories and allows preferential access to technical platforms (Mouse facility & Transgenics, Proteomics, Genomics, Imaging, Viral vectors).

The proposed research projects address three aspects of cancer: host metabolism, regulation of RhoGTPase signaling, and the role of a metalloprotease (ADAMTS-2) in tumor progression. Our lab has between 6 and 25 year experience in these research topics.

### Contract

2 years grants renewable for 2 years

### Roles and regulatory mechanisms of adipocytic lipolysis during tumour progression.

Lipid metabolism dysregulations are observed during cancer progression and are associated with an adverse diagnosis notably in mammary, prostatic and colon cancers.

Thus, lipid metabolism players are increasingly viewed as prime targets for anti-tumor therapy. We recently characterized the role of lipin-1, a key regulator of lipid storage also called phosphatidic acid phosphatase-1, in the phenotype of cancer cells. The process of lipid catabolism, also known as lipolysis in adipose tissue, is another mechanism that plays a central role in governing lipid homeostasis. It has been reported that lipolysis is part of the contribution of adipocytes to tumor growth. However, the precise contribution of adipocyte lipolysis to cancer progression in vivo and its regulation in adipocytes by tumor cells have still to be characterized. In a series of exploratory experiments, we identified G0S2 (G0/G1 Switch Gene 2), an inhibitor of the first and rate-limiting step of triglyceride lipolysis, as a regulator of adipocyte lipolysis mediated by tumor cells in vitro. The proposed program aimed at understanding the regulation and the role of adipocyte G0S2 during cancer progression. It encompasses two complementary goals: (i) To decipher the roles of G0S2 in the crosstalk between cancer cells and adipocytes in vitro and on tumor growth and metastasis in vivo; (ii) The characterization of the mechanisms triggered by cancer cells and driving G0S2 regulation in adipocytes. As a whole, our research project will precise the mechanisms triggered by cancer cells that regulate adipocytes lipolysis and the contribution of adipocyte lipolysis to cancer progression.

GIGA – Biomedical Research Center

B34, Avenue de l'Hôpital 11, Quartier de l'hôpital, B-4000 Liège

Tel +32 4 366 41 58 Fax +32 4 366 41 98

[Info.giga@ulg.ac.be](mailto:Info.giga@ulg.ac.be) – [www.giga.ulg.ac.be](http://www.giga.ulg.ac.be)

## Deciphering the RhoGDI2-specific protein interaction network and dynamics to understand its dual function in cancer.

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RhoGTPases and the factors regulating their activity are involved in several steps of tumor progression. Among the network of proteins controlling the activity of RhoGTPases, the three RhoGDIs were for a long time less studied. However, we and others demonstrated that they actively regulate the RhoGTPase signaling. Recently, several publications highlighted the peculiar properties of one of them, RhoGDI2, that displays both pro- or antitumor properties. These reports were the basis of exploratory experiments performed in our laboratory to identify mechanisms explaining the specific properties of RhoGDI2. We observed that RhoGDI2 expression is regulated by the beta-catenin/TCF pathway and that its silencing, but not the silencing of RhoGDI1, inhibits the proliferation and migration of prostate and osteosarcoma cells. Aberrant mitosis and abnormal centrosome formation and dynamics were also observed only in siRhoGDI2 treated cells. In parallel, we identified potential new interacting partners of RhoGDI2 by immunoprecipitation followed by Mass Spec analysis. The proposed project is based on our recent data and aimed at highlighting the mechanisms by which RhoGDI2 can affect cell behavior differently than RhoGDI1, and why it can display both pro- or anti-tumor properties. For these purposes, we plan to establish (i) the physical interactome of RhoGDI2; (ii) the dynamic of its subcellular localization; (iii) the functional role of the extreme N-terminal sequence of RhoGDI2 which is the most divergent domain between RhoGDI2 and RhoGDI1 and (iiii) the consequences of RhoGDI2 overexpression or silencing on tumor formation and metastases. Besides providing information about the role of RhoGDI2 itself, this study should also lead to a better understanding of the entire array of regulations modulating the functions of the whole RhoGTPase family.

*This second project will be conducted in collaboration with Prof. Marianne FILLET (CIRM, ULiege).*

## N-terminomics: a new omics in cancer

Several landmark publications and discoveries have progressively led to a better understanding of different aspects of tumor progression. A common denominator to many of the hallmarks of cancer is the critical importance of the tumor microenvironment (TME). The complex, reciprocal and dynamic nature of the interactions operating in the TME has long been underestimated. It is now clear that cancer associated fibroblasts (CAFs) can display both pro and antitumor properties, depending on the context. These cells of mesenchymal origin are responsible for the synthesis and the remodeling of the tumoral extracellular matrix and they secrete also a vast array of cytokines and metalloproteinases. There is now a plethora of studies investigating the level of expression of proteinases. Although worth knowing, such information is in essence largely insufficient since it does not say anything about their proteolytic activities on diverse substrates neither on the functional consequences of these cleavages.

Studies from our laboratory and data available in public databanks indicate that ADAMTS2, a metalloproteinase of the ADAMTS family, displays antitumor properties during the initial phases of cancerogenesis while its high expression becomes a bad prognosis marker in well-established tumors.

The aim of this project is to determine the "N-terminome" (aminoterminal extremities of proteins in a sample, "natural" or newly generated by endoproteinases) in tumor models (in vitro and in vivo) in absence and presence of ADAMTS2. Besides providing information on the substrates of ADAMTS2 and on the regulation of tumor growth by ADAMTS2, this study will be pioneering also by establishing tumoral N-terminomes. Indeed, such technological approach is not commonly used yet, while it provides a better insight into protein functions and is complementary with the other "omics" approaches in characterizing any physiopathological processes where dynamic remodeling and interactions are involved.

## Profile

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For these positions, we are looking for highly motivated and enthusiastic candidates with a strong interest in biochemistry, molecular biology and cellular biology.

Master degrees in biochemistry, molecular biology, biomedical or pharmaceutical sciences are preferred. Previous experience with classical techniques of protein biochemistry, of cellular biology and/or of molecular biology (cell culture based assays, qRTPCR, western blotting, protein purification,...) would be appreciated but not absolutely required.

## How to apply ?

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For applications or further information contact Christophe Deroanne (c.deroanne@uliege ) or Alain Colige (acolige@uliege.be)