# PhD thesis: Anti-Cancer Lectin-Clusters

Co-directed by:
Franck Fieschi (Institut de Biologie Structurale, IBS).
Olivier Renaudet (Departement de chimie moléculaire, DCM).
Jean-Luc Coll (Institut of Advanced Biosciences, IAB).

Location:
Polygone scientifique (IBS), campus saint martin d'hères (DCM) et campus santé la Tronche (IAB).

Grant: from the Glyco@Alps cross disciplinary program (October 2017 – September 2020).

**Contact:** ***Please send your curriculum (including reference for possible recommendation) and motivation letter to*** michel.thepaut@ibs.fr

**Application deadline: applications must be sent by the 14th of April 2017.**

Context: Many cellular features are modified during the carcinogenesis process and in particular the glycosylation profile of the membrane of cancer cells is deeply affected. Compared to healthy cells, specific Tn-antigens made of N-acetylgalactosamine linked by an alpha glycosidic bond to a serine or threonine (i.e. as an O-glycan) are frequently over-expressed on the surface of cancer cells. The Tn-antigens are thus excellent targets for the development of new vectors for diagnostics or treatment of tumors.

**PhD project:**

Immune cells expressing C-type lectin receptors, such as the "macrophage galactose lectin (MGL)", are already using these Tn-antigens to recognize and kill tumor cells. In this project, we will clone the carbohydrate recognition domain (CRD) of this lectin, produce it in *E. coli*, and load several copies of this CRD on artificial chemical platforms in order to generate multivalent recognition motifs. These so-called lectin-clusters will allow to target cancer cells harboring the Tn antigen on their surface and to deliver molecules of interest such as contrast agents (fluorophore…) and/or therapeutic agents (pro-drug, toxin...). At the level of a PhD, we aim at producing CDR, synthesizing these new MGL-clusters, characterizing their targeting potential and evaluating their utility as antitumor theranostic agents.

Research programs: The engineering and recombinant expression of the CRD of MGL as well as the development of an innovative coupling strategy of the protein component onto a chemical scaffold (site specific and controlled coupling) will be performed in the Fieschi's group.

Various chemical platforms displaying additional functionalization will be synthetized, optimized and characterized by the Olivier Renaudet's Team and studied using biophysical methods.

All the cellular recognition and/or internalization assays with different generation of the MGL-clusters will be performed in the group of Jean-Luc Coll, using the appropriate cancer cells and animal models. The

Protein-derived compounds will be tested for their cellular selectivity as well as their capacity to kill the targeted cells and tumors in vivo.

Expected results:

1. New functionalization methods of proteins to synthetic platforms.
2. Innovative well-defined synthetic vectors (lectin-cluster) for cell targeting and drug delivery.
3. Synthetic lectin mimetics (neolectins).
4. Cell study and cytotoxicity will be conducted after the full characterization of the MGL-clusters to determine their specific recognition and their localization by optical microscopy and flow cytometry at IAB.
5. MGL-clusters tagged with contrast agents will be tracked in tumor bearing mice using imaging techniques available at IAB (Optimal) to investigate the biodistribution and the targeting efficiency of the nano-objects.

Keywords:

C-type lectin receptor, Vectorization, recombinant protein production, biophysical characterization, solid-phase peptide synthesis, chemical ligation, cancer, drug delivery, optical imaging, diagnostics.

Candidate profile:

FR:

Nous recherchons un étudiant ayant un profil de formation tourné vers l'interface chimie/biologie. L'étudiant sélectionné pour cette thèse participera directement à la synthèse chimique d'une molécule présentatrice (scaffold) d'une part et de production de protéine recombinante (lectine) d'autre part. Il réalisera le couplage entre ces deux entités pour obtenir un bioconjugué vecteur destiné à cibler les antigènes osidiques à la surface cellulaire. Ensuite, il conduira la caractérisation moléculaire de ces bioconjugués vecteurs et l'étude biophysique des propriétés de reconnaissance (ITC, SPR, AUC). En parallèle des caractérisations biophysiques, le candidat devra mener au niveau cellulaire des études d'internalisation et de cytotoxicité (microscopie optique et cytométrie de flux). L'activité des composés les plus efficaces pourra être testé chez la souris (bio-distribution, effet anti-tumoral,...). A l'issue de ce projet, le doctorant aura acquis une formation interdisciplinaire en chimie de synthèse, biochimie/biophysique des protéines, biologie cellulaire et étude chez le petit animal.

*EN:*

We are looking for a student with a training profile at the chemistry / biology interface. The student selected for this PhD will participate directly in the chemical synthesis of a presenting molecule (scaffold) on the one hand and the production of recombinant protein (lectin) on the other hand. He will perform the coupling between these two entities to obtain a bioconjugate vector intended to target the carbohydrate antigens at the cell surface. Then, he will lead the molecular characterization of these vectors and the biophysical study of their recognition properties (ITC, SPR, AUC). In parallel with the biophysical characterizations, the candidate will have to carry out internalization and cytotoxicity studies (optical microscopy and flow cytometry) at the cellular level. The activity of the most effective compounds will be tested in mice (bio-distribution, anti-tumor effect, etc.). At the end of this project, the doctoral student will have acquired an interdisciplinary expertise in synthetic chemistry, biochemistry/biophysics of proteins, cell biology and study in small animals.

Expected results/Integration in the Glyco@Alps program:

This project will contribute to the work package 2.

It aims at developping new concept in cancer cell vectorization exploiting specific carbohydrate antigen exposed on tumoral cells.

This project fulfill the interdiciplinary requirement of the Glyco@Alps CDP pogram. It will bring togther the scientific expertise of 3 groups of carbohydrate chemistry (DCM), structural biochemistry (IBS) and cellular biology of cancer (IAB). It will be a unique opportunity for these three teams to collaborate for the first time in the field of glycosciences.

Illustrations: