Title of the thesis	Antibodies against Tumour Associated Carbohydrate Antigens
Acronym	ATACA
Reference number	020

Hosting institution	**Employer**
Université de Lille Website: https://www.univ-lille.fr/home/	CNRS Website: http://www.dr18.cnrs.fr/
Hosting research unit 1	**Hosting research unit 2**
Name: Unité de Glycobiologie Structurale et Fonctionnelle Acronym: UGSF Identification number: UMR 8576 Address: Université de Lille Cité Scientifique - Bât. C9 59655 Villeneuve d'Ascq Website: http://ugsf-umr-glycobiologie.univ-lille1.fr/	Name: Institut d'Electronique, de Microélectronique et de Nanotechnologie Acronym: IEMN Identification number: UMR 8520 Address: Cité Scientifique Avenue Henri Poincaré 59 652 Villeneuve d'Ascq Cedex, France Website: https://www.iemn.fr/
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Thesis information

Keywords	IgM; crystallography; TACA; cryo-EM; SPIONS
Abstract	Protein glycosylation has received much attention due to its many roles in normal physiological and pathological conditions. Aberrant glycosylation is increasingly being recognized as a hallmark of the epithelial mesenchymal transition. Only in the summer of 2019, paucimannosides have been definitively added to the list of aberrantly expressed glycans during cancerogenesis. Paucimannose is the tri- or dimannosyl structure of all eukaryotic N-glycans in its unsubstituted form. It is expressed abundantly in plants and invertebrates, but has been detected in only very small amounts in normal mammalian tissue. IgM antibodies display a higher diversity in their recognition of antigens than the commonly studied IgGs. Through their oligomeric form they apply the multivalent cooperative effect to specifically and with a high affinity recognize antigens. For this reason, carbohydrate antigens are generally recognized by IgM antibodies. Mannitou is a monoclonal IgM antibody that selectively recognizes paucimannosidic glycans and aucimannosylated glycoproteins. Mannitou can specifically bind human cancer tissues, adult pancreatic stem cells, inflamed mouse pancreata and colorectal cancer cells. The upregulation of paucimannosylation under embryogenic, tumorigenic and

	inflammatory conditions makes the Mannitou antibody a promising tool for diagnosis and therapy. Whole antibodies (mAbs) will be expressed in hybridoma cells and the antigen-binding fragments (Fabs) in HEK293 free-floating suspension cells. Purification of the proteins will make it possible to measure the affinities and fine-specificities for paucimannosidic ligands and set up crystallization trials of the antigen-bound Fabs to elucidate the structural basis of such interactions by X-ray crystallography at high resolution. Paucimannosylated proteins, characterized to be a biological partner of Mannitou IgM and upregulated in their expression during inflammation and cancer, will be studied in complex with the IgM using the most modern structural biology techniques, but most importantly using cryo-electron microscopy (cryo-EM). The acquired knowledge on the molecular basis of tumor suppression will be translated into applications, using superparamagnetic iron oxide nanoparticles or SPIONS, for improved glycodiagnostics and biomarker detection in glioblastomas. The research projects enholds collaborations with Dr. Diestel from the University of Bonn (Germany) for the cell biologiy of glioblastoma, and with Dr. Abrescia from CICBioGUNE (Bilbao, Spain) and Dr. Kandiah from the ESRF (Grenoble, France), for training in cryo-EM data collection and analysis. A 1-month secondment at GlycoDiag is planned, to enable progress in the development of diagnostic tools based on glycosylation. The supervision of the PhD student will occur in an interdisciplinary setting by Dr. Bouckaert, from the Unit of Structural and Functional Glycobiology, and by Dr. Boukherroub, from the Institute of Electronics, Microelectronics and Nanotechnology, in Lille. Prof. Savvides from the Center for Inflammation Research at Ghent University and the VIB (Ghent, Belgium) will be the supervisor for the successful realization of a joint PhD. This setting will help the PhD applicant, skilled in biochemistry, to become fully acquainted with high-quality structural studies of monoclonal antibodies and their applications in cancer diagnostics and therapy.
Expected profile of the candidate	Knowledge in: - Biochemistry; - solid background in Chemistry and Biology; - good knowledge of (human) Immunology; - prior knowledge of Structural Biophysical methods: crystallography, NMR and/or cryo-electron microscopy, is required; - prior knowledge of Glycobiology is a plus. The candidate is: - skilled in laboratory practices; - caring and persistent; - curiosity-driven, and strives for precision and accuracy; - strongly motivated for experimental work.
Application procedure	The application procedure is detailed on the European programme PEARL website www.pearl-phd-lille.eu. The funding is managed by the I-SITE ULNE foundation which is a partnership foundation between the University of Lille, Engineering schools, research organisms, the Institut Pasteur de Lille and the University hospital. The application file will have to be submitted before April 15, 2020 (10h Paris Time) and emailed to the following address : international@isite-ulne.fr.
Net salary and Lump Sum	A net salary of about €1,600 + €530 per month to cover mobility, travel and family costs.