PhD Project – CSC / UT-INSIA 2018

Supervisors: Dr. Yves Queneau, Co-supervisor: Dr Laurent Soulère, ICBMS-INSIA Lyon
Collaboration with Prof John W Goodby, University of York, UK and Prof Agnès Girard-Egrot, Univ Lyon.

Chemistry, structure and properties of cell membrane acyl steroid glycosides.

Abstract: The project aims at investigating the self-assembling behavior and lipid-segregation effect of acyl steroid glycosides (ASG) in relation with their role in biological membranes. It is a chemical contribution to the study of infectious or other pathogenic alterations of lipid distribution in cell membrane. This project will provide a strong chemical education in synthetic organic chemistry, together with a transdisciplinary experience in the frame of our collaborations with other groups in France and abroad at the interface of physical and biochemistry.

In cell membranes, within the lipidic bilayer organisation, glycolipids establish low-energy interactions with cholesterol to form microdomains in which many eminent biological events take place. Examples of alterations due to infectious diseases or age-associated decline and dysregulation of cellular signaling pathway have been demonstrated. Cholesterol distribution and cholesterol interactions with other membrane components appear as a key issue.

One interesting type of complex glycolipids are systems comprising a carbohydrate, a steroid and a fatty chain, referred to as acyl steroid glycosides (ASG), such as the β-galactoside BbGL-1 or the α-glucoside α-CAG that are found in the membranes of the pathogens Borrelia burgdorferi, the etiological agent of Lyme disease, and Helicobacter pylori, bacteria suggested to be related to gastric malignancies respectively. Looking more closely at these systems, they only differ by limited structural modifications (glucose or galactose, α or β glycosidic bonds, chain length of the 6-O-fatty ester). Why Nature makes such structural choices? What are the consequences in terms of lipid segregation and membrane physicochemistry? This is what we have started to investigate recently by studying the supramolecular behavior of these systems and their analogs.

Because cell membranes are complex systems in which various types of molecules, including glycolipids, self assemble and self organize, finally establishing liquid crystalline systems with high level of organization, one approach is to investigate the liquid crystalline properties of ASGs. Our group in association with Prof. John W. Goodby, FRS, University of York (UK), has developed fundamental research on liquid crystalline glycolipids. We have also investigated biomimetic glycolipid probes as membrane imaging systems. Here again in this project, part of the investigations will be performed in close collaboration with the York group, following the recent preliminary work reported this year.
Supramolecular constructs exhibiting thermotropic or lyotropic liquid crystal properties at room temperature or having auto-associative behaviour in biological media are of great interest in the context of advanced materials and sensors, interactions with cell membranes, and targeted drug delivery systems. This project will focus on the rational design, synthesis, and characterisation of the physico-chemical properties of novel supramolecular systems involving carbohydrates, in particular ASGs.

In this project is also associated a team of biochemists within ICBMS in Lyon for investigations of the way ASGs drive the lipid segregation and domain formation within the membrane, with the aim of determining the key structural parameters responsible for lipid segregation. This team is led by Prof Agnès Girard-Egrot, a renowned specialist of model biomimetic membranes through Langmuir monolayer investigations.

Previously, we designed some complex bolaphilic glycosteroid hybrids and prepared them by the CMGL strategy (Fig. 1) developed in our lab and used in several applications in glycosciences. These materials were found to exhibit very unusual phase behaviour as upon heating they form one set of phases but on cooling another phase sequence is found. This result shows that these liquid crystal phases are kinetically rather than thermodynamically stable, and could therefore in principle co-exist. For cell membranes, this implies that other phases, such as the cubic phase, can co-exist with the lamellar bilayer structure. It has been suggested that these types of mesophase co-existence may provide the conditions whereby infection might spread. Naturally occurring compounds with analogous structures have been found to interfere with membranes during an infection process.

![Fig. 1. CMGL-based first generation of hetero-dilipidic glycosteroid hybrids](image)

Since, we have proposed a new vision and classification is for complex glycolipidic systems comprising a steroid moiety, differentiating their polarity and amphiphilicity pattern: amphiphilic polar-non-polar systems (carbohydrate-steroid, CS), possibly connected by a spacer (CspS), bolaphilic systems, either carbohydrate-steroid-carbohydrate (CSC) or steroid-carbohydrate-fatty chain (FCS). This latter class corresponds to the acyl steroid glycosides (ASGs) family, to which belong very interesting components of pathogenic bacterial membranes (such as *B burgdorferi* or *H. pylori*).
This PhD proposal will focus on the study of these naturally occurring and biologically relevant membrane components and their analogues, combining synthetic organic chemistry, materials science and biochemical and physicochemical investigations in model membranes, thus providing a very multidisciplinary frame of doctoral education within highly experienced and renowned teams.

The synthetic work will rely on the very strong expertise in carbohydrate chemistry which is the specialty of Yves Queneau, a renowned carbohydrate chemist. As for the liquid crystalline behavior, the materials will be investigated at York in a variety of ways thermal polarised microscopy in their neat forms, and then with the addition of water, differential scanning calorimetry and ultimately x-ray diffraction). The compounds will also be studied as for their behaviour when mixed with biomembranes. Additional decoration with a fluorescent tag could allow specific imaging of some cholesteryl rich zones in membranes. Biochemical studies will be conducted in biochemistry teams in ICBMS in Lyon.

Glycosteroids are extremely interesting compounds which exhibit a wide range of properties, some of them being related to traditional medicine. It is anticipated that this project will lead to innovative glycosteroidal architectures with high biological relevance, provide new visions in the behavior of glycolipids and their interactions with cholesterol, and improve the knowledge of lipid distribution in membranes in relationship with infectious diseases and age-dependent dysfunctions.

Though the project is primarily a chemical approach, associated with materials science and biochemical investigations, the ultimate goal of this project is to understand the physicochemical contribution in the biological role (physiological or pathological) of such molecules, to bring novel knowledge on the biochemistry of such complex acyl steroid glycosides, and therefore to provide new concepts for targeting the pathologies which are associated.

This project will provide a strong chemical education in synthetic organic chemistry, together with a transdisciplinary experience in the frame of our collaborations will other groups in France and abroad at the interface of physical chemistry and biochemistry.

References.


Required background, benefit for the candidate:

The work will be conducted in Lyon, within the team specialized in synthetic organic chemistry, which is the heart of the project. The candidates must possess a strong background in synthetic organic chemistry. Experience in carbohydrate chemistry and/or at the interface with biology will be appreciated but is not mandatory. A good motivation to learn, communication skills, curiosity, and good team spirit are also among important qualities. Some knowledge of English is also important.

The work will involve various sectors of organic chemistry, notably multistep carbohydrate chemistry. While focusing on synthetic organic chemistry, the project, which stands at the frontier with physical chemistry and biochemistry, will be achieved in close collaboration with colleagues in materials sciences and biochemistry, in France and abroad. The candidate will therefore benefit from a transdisciplinary education in organic chemistry and related disciplines, ranging over chemical and biological sciences. A precise work plan will be given to the PhD candidate and careful supervision of his/her will be organized, with regular work meetings and written reports.

Description of the laboratory:

The team Chimie Organique et Bioorganique of INSA is part of the ICBMS (http://www.icbms.fr/), the biggest research unit in synthetic and biological chemistry of the Lyon university. Our team (http://www.icbms.fr/cob) is well known for its contributions in biological chemistry and carbohydrate chemistry. In the end of 2017, the lab will move into its new facilities, in a brand new building presently under construction in the frame of the LyonTech La Doua project. The PhD student will thus profit from state-of-the-art laboratories and facilities for his/her thesis work.
Dr Yves QUENEAU’s CV:

Dr Yves Queneau (55 yo) is a CNRS Research Director (Equivalent to Research Professor) and Head of the COB Team, the INSA-Lyon part of the Institut de Chimie et Biochimie Moléculaires et Supramoléculaires (ICBMS), deeply involved in chemistry at the interface with biology. He graduated from the University of Paris-Sud (Orsay) in 1988, where he received his Ph.D under the supervision of Professor André Lubineau. Appointed as CNRS fellow in 1988, he then spent one year in Prof Samuel Danishefsky’s group in New York, USA (1991). He later moved to Lyon in a mixed CNRS-industrial research facility dedicated to carbohydrate chemistry where he was promoted to a Research Director in 1995. In 2003, he joined the University of Lyon, where he is head of the INSA part of the Institut de Chimie et Biochimie Moléculaires et Supramoléculaires (ICBMS) and leads the team Organic and Bioorganic Chemistry. In 2007, he was promoted to a Research Director 1er Class and since 2009, he is also appointed as Honorary Professor at the University of Hull (UK). He teaches carbohydrate chemistry in several universities. He was awarded the CNRS Bronze Medal in 1994 and the “Europol’Agro” Prize for Scientific Innovation in 1998 and is among the recipients of the 2010 and 2014 CNRS rewards for scientific excellence and doctoral supervision. He develops his research in carbohydrate chemistry and bioorganic chemistry and has published more than 130 papers, book chapters and patents in his career. He serves as member in many panels and committees as well as referee for numerous journals, and is a member of the board of editors of the book series Specialist Periodical Reports of the Royal Society of Chemistry for the “Carbohydrate Chemistry, Chemical and Biological Approaches” series.

Over the last 10 years, Dr Queneau made regular visits to China and has developed collaborations and shared the responsibility of scientific meetings with Prof HUANG Peiqiang (Xiamen), Prof HE Mingyuan in ECNU (Shanghai), and Prof GU Yanlong in HUST (Wuhan). He notably co-chaired the recent French-Chinese conference on Green Chemistry (www.FC2GChem.org) in Wuhan and Shanghai in Nov 2014 and in Lyon in 2016, and preparing the next event in China in 2018. He was guest editor in chief of special issues in Comptes-Rendus Chimie in 2008 and in Science China Chemistry in 2010 dedicated to collaborations in chemistry between China and France. He has delivered several conferences in Beijing, Shanghai, Wuhan, Guangzhou, Xiamen in the past ten years and also taught some carbohydrate chemistry in Shanghai and in Wuhan. In 2015 he was awarded the LU Jiaxi lecture award by the College of Chemistry and Chemical Engineering of the University of Xiamen.

Dr Laurent SOULERE’s CV:

Laurent Soulère has received his PhD in the University of Toulouse in 2001 under the supervision of Professor Périé. He then spent 18 months as post-doctoral fellow in the group of Pr. Waldmann at the Max Planck Institut for Molecular Physiology in Dortmund, Germany, and one more year in the laboratory of environment and biomolecular chemistry at the University of Perpignan, France. In 2004, he was appointed as assistant professor at the ICBMS, INSA Lyon, in the team Organic and Bioorganic Chemistry. He has strong expertise in the design of biologically active molecules and computational methods, including virtual screening, and molecular modelling. He has published 40 articles in the field, notably on QS modulation. Dr Soulère is among the recipients of the 2009 and 2014 rewards for scientific excellence and doctoral supervision from INSA Lyon. He develops collaborations with biologists and biochemists in France (Lyon, Grenoble and Gif) and in Chile (Santiago) with projects dedicated to new antibacterial and anticancer strategies.

Contacts:
Dr Yves QUENEAU,
Research Director, CNRS, Head of ICBMS INSA Lyon.
yves.queneau@insa-lyon.fr Tél : + 33 (0)4 72 43 61 69