# Une image contenant assiette  Description générée automatiquementlogo_lienss2.jpgphD offer – UMR LIENSs- La Rochelle Université

***Applications of marine Oligosaccharides in Nanomedicine strategies against cancer***

## **Start of the phD :** 1st October 2021 (2021-2024) – Fixed-term contract with La Rochelle University with graduate school EUCLIDE (Funding : Région Nouvelle-Aquitaine/Ligue contre le Cancer)

## **Host laboratory :** UMR 7266 - CNRS - LIENSs – director : Pr. Olivier De Viron

## **Host research team :** Biotechnologies et Chimie des Bioressources pour la Santé (BCBS)

**Supervisor of the phD :**

Supervisor - Pr. Ingrid ARNAUDIN : 05.46.45.85.62 /ingrid.fruitier@univ-lr.fr

Co-supervisor - CRCN Hugo GROULT : 05.46.45.82.77 / hugo.groult@univ-lr.fr

**Application as soon as possible :** Applicants have to send their request to Ingrid Arnaudin (ifruitie@univ-lr.fr) and Hugo GROULT (hugo.groult@univ-lr.fr)

The applications must include the following documents: CV, cover letter, transcript of grades of the two last years and reference letter.

**Scientific context of the phD**

It is widely appreciated that nanomedicine is currently one of the best strategies for medical research, especially in oncology. An important part of its research is devoted to the development of **multifunctional nanoparticles (NP)** for **targeted drug delivery** or else as **imaging tools** for both, advanced therapeutic and diagnostic applications. However, even if huge progress has been made in the field these last decades and several products arrived on the market, **many obstacles remain to be addressed** toward full utilization of these powerful NP in the clinic and **to improve their translational value**.In this context, the BCBS team of LIENSs laboratory is studying **innovative coatings made of natural oligosaccharides (OS) combined with a new generation of extremely small iron oxide nanoparticles (ESIONP) for the development of targeted and personalized therapy against cancer.**

**These innovative OS coatings** may answer **new considerations for successful development of multifunctional NP,** especially in: **i) reaching renal clearance pathway** (to avoid toxicity issues from endogenous metabolization) ; **ii) targeting and the regulation of tumor microenvironment’s biomarkers** (today favoured to increase the selective accumulation of NP and produce a therapeutic effect because they are easily accessible); **and iii) fulfilling various advanced functions simultaneously** (to propose simplified nanoformulation promoting easy synthesis and possible high-scale GMP production)**.** **The ESIONP** have been selected because they can provide **a diagnostic function**. Compared to the previous use of iron oxide NP as negative contrast agent for magnetic resonance imaging (**MRI**), this new generation (based on magnetic cores <5 nm) has been developed to provide **a positive contrast**. This contrast makes these probes closer to the current clinical practices for MRI-based diagnosis. Furthermore, these ESIONP can be **easily upgrade for PET/SPECT imaging** without altering the coating **by a doping of the magnetic core** with a radioisotope (68Ga, 67Ga, 64Cu) during the synthesis. These highly advanced reporter probes can be advantageously exploited, allowing by a single procedure of medical imaging to verify the accumulation in tumor and give a predictive outcome of the suitability of the treatment. Thus, they answer the **4th challenge for the development of NP, which is personalized medicine.** Lastly, when they are not used as contrast agents, a fresh research is interested in the **ESIONP capacity to produce a positive immunomodulation** on the tumor-associated macrophages.

This research relies on the common use of native **polysaccharides (PS)** (ie the raw macromolecules directly extracted from the natural ressources) in the NP’s formulations. In nanomedicine, **PS are commonly used as stabilizing coating in the NP architectures**, appreciated to provide good colloidal stability, to ease the conjugation/encapsulation of biomolecules with a specific function (targeting, drugs, linker,…) and to establish controlled release systems. PS also gained interest as targeting ligand and even as the proper therapeutic agent of the nanoformulation. However, their **high MW often coupled with heterogeneous and complex structure afford NP of uncertain *in vivo* behaviour**, with unsuitable pharmacokinetics (PK) properties that limit the applications (short blood lifetime, hepatic clearance leading to toxicity issues because of endogenous metabolization). Another important issue is their **multiple bioactivities, frequently causing secondary or serious adversary effects**. This **locks-up the uses to only a small number of species** among the wide variety of existent polysaccharides, whom some could yet have great potential. **The BCBS team is expert in the synthesis of oligosaccharides (OS), which are the low-molecular weight derivatives of PS** prepared by depolymerisation techniques.[1,2] The controlled synthesis with post-modification possibilities and easier purification processes leads to **much more defined molecular structures and biological properties**. This may **warrant a better control of the NP *in vivo* behaviour**. The key point is it could **open the uses to other variety of PS,** moved aside because of undesirable bioactivities in their native form, but whose OS derivatives are released.

These last years, the BCBS team worked especially on heparins polysaccharides. First, we developed a method for the preparation of ESIONP functionalised by heparin coatings (HEP-ESIONP). HEP-ESIONP have been shown to maintain the intrinsic biological activities of heparins (anticoagulant and anti-tumoral through inhibition of the pro-tumoral enzyme called heparanase) and to display *in vivo* positive contrast in MRI.[3] The BCBS team next achieved a study about the impact of the size of heparin oligosaccharides (OS[HEP]) on the PK and tumor accumulation of the NP, in particular thanks to PET-based *in vivo* biodistribution analysis and proteomic analysis. This study highlighted significant changes in the probe behaviours according to the size of the OS[HEP]. It identified a precise length for the OS coating to ensure a good vascular lifetime, a predominant renal clearance and a moderate tumor accumulation.[4]

**Objectives of the phD**

In the roots of these last results, we propose a phD projet to continue the research on the HEP-ESIONP and open the strategies on two new families of polysaccharides: the **λ-carrageenans** and the **ulvans.** This project is part of national and international networks. Especially it is enclosed in a close collaboration with the biomaterials center of excellence CICBiomagune (San-sebastian, Spain), where the candidate will make one or several academic stays (possibility of European mention)

**The candidate will have in charge the synthesis and characterizations of oligosaccharides-based nanoformulations and their *in vitro* and *in vivo* evaluations in murine models.**

**Methods and tasks of the phD candidates**

Specifically, the candidate will carry on :

**1) The synthesis and purification of OS from native PS (heparin,** **λ-carrageenans and ulvans).** He/she will use enzymatic or chemical methods of depolymerisation already published by the team and the chromatography platform of the lab for the purification.

**2) The synthesis and physicochemical characterization of OS-based NP.** First, the synthesis used will be a microwave method already published by the team. One of the 1st work of the candidate will be the optimization of this method to a green ecological process. Physicochemical characterizations will include: hydrodynamic size measurements by DLS and core size measurements by TEM, surface charge measurements by Z-potential, determination of NP concentration and OS content, TGA analysis, IR spectroscopy, and magnetic measurements. First ranges of biological activities will also be conducted (colorimetric and/or fluorescent assays to determine enzymatic activities).

**3) Achieve structre/function studies on the impact of the size/or positive charge modulation of the OS coatings on the PK and tumor accumulation of the NP.** For this, the candidate will use OS of different lengths (by controlling the depolymerisation time) and will include in the nanoformulations minor fractions (< 10%) of chitosan oligosaccharides, a natural sugar positively charged. Evaluation of the vascular lifetime, tumor accumulation and clearance pathways will be achieved by PET-based *in vivo* biodistribution studies in mice, using the advance reporter probes (integrating the radioisotopes) in collaboration with the CICBiomagune (San Sebastian, Spain).

**4) Validate the anti-tumor pharmacological properties against selected carcinoma.** The candidate will perform *in vitro* cell experiments of the best NP candidates (cytotoxicity, migration, invasion, angiogenesis) on breast (MDA-MB-231) and hepatic (Huh-7) cancer cells to evaluate the bioactivities coming from the grafted OS. The candidate will perform also *in vitro* cell experiments (Inflammatory markers, phagocytic activity) on macrophages cell line to evaluate the immunomodulatory effects coming from the iron oxide core. According to the advances and results, a therapeutic assay in a murin model could be considered.

The candidate will be in charge of the data curation, statistical analysis, editing and discussion regarding the literature. He/she will communicate these results to a large audience in scientific international conferences but also scientific events of vulgarisation.

**Skills required for the candidates**

The candidates shall have a **master’s degree of research in chemistry** (therapeutic chemistry, chemistry of biomolecules or nanomaterials) **or in biochemistry** with a good knowledge of natural compounds. An experience or specialization in nanoscience or cell culture will be an advantage for the application. The candidate should have a good interest for cancerology, bench experiments and small animals handling. Good skills in English and in scientific writing are mandatory.

Salary : ~1400 €/net

**References**

1. Groult H, Cousin R, Chot-Plassot C, et al. λ-Carrageenan Oligosaccharides of Distinct Anti-Heparanase and Anticoagulant Activities Inhibit MDA-MB-231 Breast Cancer Cell Migration. Mar Drugs. 2019; 17: 140.

2. Poupard N, Groult H, Bodin J, et al. Production of heparin and λ-carrageenan anti-heparanase derivatives using a combination of physicochemical depolymerization and glycol splitting. Carbohydr Polym. 2017; 166: 156–65.

3. Groult H, Poupard N, Herranz F, et al. Family of Bioactive Heparin-Coated Iron Oxide Nanoparticles with Positive Contrast in Magnetic Resonance Imaging for Specific Biomedical Applications. Biomacromolecules. 2017; 18: 3156–67.

4. Groult H, Carregal-Romero S, Castejón D, et al. Heparin length in the coating of extremely small iron oxide nanoparticles regulates *in vivo* theranostic applications. Nanoscale. 2021; 13: 842–61.