PhD THESIS ALLOCATION OFFER

ÉCOLE DOCTORALE SCIENCES EXACTES ET LEURS APPLICATIONS - ED 211 / NATURAL SCIENCES DOCTORAL SCHOOL

Avenue de l'université BP 1155 64 013 PAU Cedex – France

PhD THESIS SUBJECT

TITLE

Marine-origin polymers to develop hydrogel scaffolds for drug testing

ABSTRACT

This PhD program will create novel hydrogels from marine biomass. Hydrogels are widely used for 3D cell culture but current hydrogels have major drawbacks. To overcome these problems, hydrogels based on marine biopolymers (e.g., from fish, crustaceans and micro- and/or macro-algae) will be synthesize and derivatize conferring the required biological and physical properties to support the growth of specific tumor cell types. The focus will be on developing hydrogel scaffolds, in particular using marine polysaccharides or proteins, that can be scaled up for use in drug testing using automated 3D printing technology.

The thesis will be divided in 3 main research axes: i) the design and synthesis of multiscale structured 3D hydrogel scaffolds based on marine polymers reinforced with different sources of nano- or microparticles through different approaches like the classic freeze-drying and phase separation methods; ii) the assess of the optimal hydrogel(s) by the characterization of the physicochemical, morphological, mechanical and biological properties; and iii) the assess of the scale up capacity of the hydrogels for its use in drug testing using automated 3D printing technology.

This PhD program is part of a collaborative project, in the framework of the Interreg Atlantic Area programme, calls *BOTS (Blue Organoids for Treatment Selection)* between 6 research teams from France, Spain, Portugal and Ireland. In particular, the recruited candidate will be part of the Research Chair MANTA: Marine Materials (IPREM, E2S UPPA, https://iprem.univ-pau.fr/fr/collaborations/chaires/manta.html).

Keywords: marine biopolymers; natural polymers chemistry; hydrogels; development 3D biomaterials; (bio)mineralization; biomimicry; mechanical and biological properties

CONDITIONS D'EXERCICE

Laboratory:

- Institut des Sciences Analytiques et de Physico-chimie pour l'Environnement et les Matériaux (IPREM UMR 5254, CNRS and Université de Pau et des Pays de l'Adour, Pau, France)

Site web: https://iprem.univ-pau.fr/fr/index.html

Thesis supervisor : Pr Susana Fernandes (IPREM-Pau)

Susana Fernandes is Professor and Chair in Marine Bio-inspired Biomaterials (MANTA), IPREM, UPPA, France. She is expert in natural polymers, in particular from marine biomass. She has over 13 years of experience in polymeric materials from renewable resources, acquired at the interface of chemistry, biology, biotechnology and material science, and establishing a track record of solid contributions to the field. Her research is based on the chemistry of carbohydrate-based materials, chemoenzymatic modification of biopolymers, processing and characterization of polysaccharide-based (nanocomposite) materials and biorefinery by green extraction of biopolymers - cellulose, chitin & collagen nanofibers - and secondary metabolites. She dedicated particular effort to understanding the bioactive protection of biological materials in marine ecosystems, and connecting it to multifunctional & sustainable (bio)materials - using bio-inspired synthesis & design principles.

Place: Pau, France

Starting Date: February/Mars 2024	**Durée:** 3 years
Employer: UPPA	
Gross monthly salary: 2131 € (UPPA doctoral contract)	

DESCRIPTION OF THE LABORATORY

IPREM (https://iprem.univ-pau.fr/fr/index.html): The Institute of Analytical Sciences and Physico-Chemistry for Environment and Materials (IPREM) is a Joint Research Unit CNRS / UPPA (UMR 5254). IPREM members are interested in the development of fundamental knowledge in physico-chemistry, analytical chemistry and microbiology, in relation to applications concerning the structure of the living, the management of the environment and the functional properties of different classes of materials. Chimie Analytique, Physique et Théorique, Physico-chimie des matériaux, Chimie et Microbiologie de l'Environnement. In particular, our team activities mainly concern the synthesis and elaboration of marine materials, their physico-chemical characterization, the their chemoenzymatic synthesis or functionalization, and the understanding of the relationship between their structure and properties on several scales.

MISSION – PRINCIPALS ACTIVITIES

I. Scientific context & Implementation

The blue bioeconomy can provide multiple, significant services towards meeting global challenges, in particular, health for all and biomaterials. Marine biodiversity - with about 250 000 known species and many more to be discovered - is a critical factor with regard to all three pillars of sustainable development – economic, social and environmental. In particular, marine biological materials play a key role in the blue bioeconomy. They could replace fossil-based materials and make a positive contribution to the mitigation of climate change and the sustainable use of natural resources. Several marine products end up as waste that could be used for the extraction of natural polymers and bioactive small molecules contributing to minimize waste and conserving natural resources in the long-term. According to the Food and Agriculture Organization of the United Nations, in 2018 global of fisheries and aquaculture production was 178.5 million tons (10% from European production). Out of this vast amount, more than 50% of the total weight ended up as by-products, including crustacean exoskeletons (carapaces), and fish bones, skin and scales and algal biomass. Extracted macromolecules such as collagen, chitin, agarose, carrageenan, porphyran and alginate are fascinating and promising by-products that have stimulated progress in many fields of applied science worldwide (1-7). They fulfil current demands for availability, sustainability, biocompatibility, functionality, renewability, biodegradability, social acceptability and industrial applicability.

In this context, this project will create new hydrogels from marine biomass. Hydrogels are widely used for 3D cell culture but current hydrogels have major drawbacks. To overcome these problems, we will synthesize hydrogels based on biopolymers from marine biomass like fish, crustaceans and algae, and functionalize them with other natural molecules and/or inorganic compounds to support the growth of specific cell types and confer the biological and physical properties necessary for bioprinting. We will focus on marine biological materials for three reasons: as a source of fundamental knowledge based on understanding their structure-function relationships; as a source of inspiration for making biomimetic biomaterials; and as a source of biomass containing natural polymers like chitin, hyaluronic acid, cellulose, alginate, agarose and collagen from fishery by-products. Marine organisms are a major source of biomaterials and bioactive natural products as they produce molecules (enzymes, natural polymers, peptides, carbohydrates, bioactive compounds, secondary metabolites) that can find applications as pharmaceutics, antibiotics, antifouling products and biomaterials. Marine natural polymers, like proteins and polysaccharides, have been used to make hydrogels because of their structural, rigidity, bioadhesive, biocompatible and functional properties. Furthermore, bioactive compounds and secondary metabolites

have been linked to macromolecules in hydrogels to exploit their antioxidant, antimicrobial and anticoagulant properties (1-7).
The hydrogels will be made using marine proteins like collagen from fish scales, jellyfish, starfish, sea cucumbers; or marine polysaccharides like hyaluronic acid, chitin, cellulose extracted *in-house*. Gelation will result from chemical linking (chemical hydrogels, linked by covalent bonds). Chemoenzymatic approaches will be used, and the crosslinking agents will be essentially commercial, but we will also use new non cytotoxic marine crosslinkers that have been developed by UPPA. In terms of physical appearance, the hydrogels can be in the form of a matrix, film, microsphere, or 3D porous scaffold, depending on the processing method (casting-evaporation, freeze-drying, etc). The ensuing marine natural biomaterials and the marine-based hydrogels will be characterized in terms of their physico-chemical, morphological, mechanical and thermal properties. UPPA has outstanding infrastructure and technical platforms (UPPAtech, https://uppatech.univ-pau.fr/fr/index.html) for the development of experimental methods and for characterization of small molecules, macromolecules, and polymeric and hybrid materials. These biomaterials will be characterized using Fourier Transform Infrared Spectroscopy (FTIR), nuclear magnetic resonance (NMR) and time of flight secondary ion mass spectrometry (Tof-SIMS) to know their chemistry in bulk and surface. SAXS and WAXS will be also used, if pertinent for physical characterization. The morphology will be analyzed using atomic force microscopy (AFM), scanning electron microscopy (SEM), optical microscopy, and x-ray tomography for 3D visualization and analysis of internal and external morphology of the hydrogel. The mechanical properties will be evaluated using rheology and tensile and/or compression tests. Swelling tests will also be performed.

II. Objectives

The main objective of the project is to develop marine hydrogels derived from marine biopolymers for 3D culture of cells. The marine hydrogels will be chemically modified to support the growth of human cells and to confer the physical properties required for bioprinting. This will ensure that they can be scaled up for commercial use.
The specific objectives (SO) are:
SO 1) To design and synthesis of multiscale structured 3D hydrogel scaffolds based on marine polymers reinforced with different sources of nano- or microparticles through different approaches like the classic freeze-drying and phase separation methods;
SO 2) To adapt marine hydrogels for organoid culture requires covalent attachment of ligands and chemical modifications to change the adhesive and viscoelastic properties of the hydrogels to promote the survival and proliferation of cells;
SO 3) To assess of the optimal hydrogel(s) by the characterization of the physicochemical, morphological, mechanical and biological properties;
SO 4) To assess of the scale up capacity of the hydrogels for its use in drug testing using automated 3D printing technology.

Expected results:

- Fundamental knowledge on marine-based hydrogel scaffolds for 3D cell culture (survival and proliferation of cells).
- Understand the chemical reactions involved to avoid producing a hydrogel that is toxic to living cells.
- Characterization of the new hydrogels.
- Optimized processes for the scale up of novel hydrogels scaffolds for 3D cell culture of interest.
- Innovation in the blue bioeconomy: healthcare & pharmaceutical applications by creating new uses for marine biomass.
- Publication in high impact factor journals and possible patents due to the novelty of the approach envisioned.

IV. References

1. Zhu, et al.. *Sustainable polymers from renewable resources*. Nature. 540**,** 354 (2016).
2. M. Claverie, C. McReynolds, A. Petitpas, M. Thomas, S.C.M. Fernandes. *Marine Polymeric Materials and Biomimetics: an overview*. Polymers. 12, 1002 (2020)

3. V. Zubillaga, A. M. Salaberria, T. Palomares, A. Alonso-Varona, S. Kootala, J. Labidi, S.C.M. Fernandes, *Chitin nanoforms provide mechanical and topological cues to support growth of human adipose stem cells in chitosan bionanocomposite matrices*, Biomacromolecules. 19 (7), 3000–3012 (2018)
4. V. Zubillaga, A. Alonso-Varona, S.C.M. Fernandes, A.M. Salaberria, T. Palomares, *Adipose-derived mesenchymal stem cell chondrospheroids cultured in hypoxia and a 3D porous chitosan/chitin nanocrystal scaffold as a platform for cartilage tissue engineering*, International Journal of Molecular Sciences. 21, 1004 (2020)
5. F. Samalens, M. Thomas, M. Claverie, N. Castejon, Y. Zhang, T. Pigot, S. Blanc, S.C.M. Fernandes, *Progresses and future prospects in biodegradation of marine biopolymers and emerging biopolymer-based materials for sustainable marine ecosystems*, Green Chemistry. 24, 1762 (2022)
6. S.C.M. Fernandes, G. Aguirre, *Biopolymer Micro/Nanogel Particles as Smart Drug Delivery and Theranostic Systems*, Pharmaceutics. 15, 2060 (2023)
7. S. Olza, A.M. Salaberria, A. Alonso-Varona, A. Samanta, S.C.M. Fernandes, *The role of nanochitin in biologically-active matrices for Tissue Engineering – Where do we stand?* Journal of Materials Chemistry B. 11, 5630–5649 (2023)

REQUIRED SKILLS

The candidate should have experience and knowledge in (bio)polymer chemistry and/or marine polymers; and/or biochemistry and/or molecular biology; biomaterials chemistry; biostatistic. He/she will be able to conduct and manage biopolymer modification strategies by conventional and biotechnological routes, develop hydrogel-based materials, perform *in vitro* biological and physico-chemical characterization of biomaterials, and analyse data. The candidate will demonstrate multidisciplinary work skills, scientific rigour, a good scientific English writing and speaking and a good ability to communicate in French and English.

APPLICATION EVALUATION CRITERIA

Selection Process:
- Constitution of a Jury.
- Selection of candidates on the basis of their application file.
- Applicant's audition and ranking.

Criteria for the application evaluation:
- Motivation, scientific maturity and curiosity.
- Knowledge in biopolymer/polysaccharide chemistry/ hydrogels/ biomaterials/physic-chemical characterization materials.
- Ranking in Master1 and Master2.
- Mastery level of the English language.

CONSTITUTION OF THE APPLICATION FILE

Send by email an application file including:
- CV
- Letter of motivation
- Master's report cards and rankings
- Summaries of M2 internship + other internships (if appropriate)
- Reference letter(s)
- Contact details of people in the professional field (minimum two)

DEADLINE	**26/1/2024**

CONTACTS

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