EU-DOCS for SmUCS

CO-SUPERVISED SUBJECT PROPOSAL FOR A DOCTORAL CONTRACT

Title of the thesis project: Development of bio-based antiviral materials based on biopolymers and marine bacteria-derived compounds for biomedical applications	
La Rochelle University Research Unit: LIENSs (LIttoral ENvironnement et Sociétés)	**Partner university:** Catholic University of Valencia (UCV), Spain **Cotutelle research unit:** Biomaterials and Bioengineering Laboratory
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Non-academic partner: ProtoQSAR (Spain)- 3rd year of PhD	
Keywords *(6 max)*: antiviral, biomaterials, marine bacteria, alginate, chitosan.	

Scientific description of the research project

Scientific Context

Viruses continue to pose a significant threat to global public health, being one of the leading causes of mortality worldwide, responsible for millions of deaths every year, as exemplified by recent pandemics [1,2]. The primary approach to clinical antiviral therapy involves the use of antiviral drugs alongside symptomatic treatments. However, significant side effects from antiviral drugs, such as gastrointestinal, liver, kidney, or hematopoietic issues, can impact patient adherence and potentially disrupt treatment. Additionally, frequent viral mutations and the limited scope of single antiviral mechanisms can result in drug resistance, often causing therapeutic failure [3,4]. The incorporation of biomaterials, such as alginate and chitosan, into antiviral therapy offers distinct benefits and novel mechanisms of action. Antiviral biomaterials function through a variety of mechanisms, including physically adsorbing viruses, interference with the virus–cell interaction by binding to the viruses as entry inhibitors, inducing irreversible viral deformation, interfering with viral nucleic acid replication, and preventing the release of viruses from infected cells, among other mechanisms. The capture of viruses through virus–biomaterial interactions and the disruption of viral structures via applied forces represent distinctive antiviral mechanisms of biomaterials. Therefore, biomaterial-based antivirals further offer new mechanisms and reduce the risks of developing drug resistance, which can be observed widely in molecular antivirals [5]. In this regard, numerous biomaterials are being designed in combination with antiviral drugs against a range of viral infections [6,7]. Interestingly, various biomaterial formulations have demonstrated higher efficiency in inhibiting viral nucleic acid replication compared to conventional antiviral drugs [8]. Therefore, there is an urgent demand for novel antiviral materials that offer effective prevention and control of viral infections, especially in the context of biomedical applications [3,4].

The marine environment represented a largely unexplored habitat [9]. Due to the abundance and chemical composition of marine compounds, this environment represents a significant reservoir of original biomolecules. Marine species, both prokaryotes and eukaryotes, synthesize numerous metabolites belonging to various structural classes, such as sugars, pigments, lipids, proteins,

polyketides, alkaloids, steroids, etc. The biological activity of these compounds is highly promising for the development of new drugs derived from natural marine organisms. Among these original compounds, some are derived from marine bacteria, which are a rich source of molecular diversity [8]. Their adaptation to extreme and often competitive environments promotes the development of specific metabolites. As a result, these bacteria remain among the most promising microorganisms for the discovery of new molecules with unique properties, including antimicrobial, anticancer and antiviral activities. Therefore, marine bacteria represent a promising and underexplored source of bioactive metabolites with potential antiviral properties.
By leveraging these metabolites and combining them with biocompatible biopolymers like alginate and chitosan, this PhD thesis project aims to develop antiviral materials capable of mitigating viral infections while maintaining safety and functionality in biomedical contexts.

References
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[3] Serrano-Aroca et al. Advanced Functional Materials 2024, 34 (38), 2402023
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[5] López-Labrador et al., Future Microbiology 2015, 10 (11)
[6] Lembo et al., Antivir. Chem. Chemother. 21, 53–70.
[7] Singh et al. Viruses 2018, 10(5), 267
[8] Paoli et al. Nature 2022, 607, 111–118
[9] Chen et al. Nature 2024, 633, 371–379

Scientific Objectives
The main objective of this PhD thesis is to develop, characterize, and evaluate antiviral materials for biomedical applications using bioactive metabolites extracted from marine bacteria from La Rochelle Collection. The specific objectives are as follows:

1. Isolation and identification of antiviral metabolites by extracting and characterizing bioactive compounds with antiviral activity from marine bacterial cultures.
2. Formulation of antiviral materials by developing composite materials by incorporating the identified metabolites into alginate and chitosan matrices, ensuring uniform distribution and stability of the bioactive agents.
3. Evaluation of antiviral efficacy by assessing the antiviral activity of the developed materials against a range of viral pathogens, with emphasis on clinically relevant strains.
4. Characterization of material properties by evaluating the physicochemical, mechanical, and biocompatibility properties of the developed antiviral materials to ensure they meet biomedical standards.
5. Mechanistic studies by investigating the mechanisms underlying the antiviral activity of the developed materials to elucidate their modes of action.

Scientific Challenges
The project entails several scientific challenges:

1. Extraction and stability of marine-derived metabolites by ensuring efficient extraction, purification, and stability of bioactive metabolites from marine bacteria, while maintaining their antiviral efficacy during processing and integration with polymers.
2. Material formulation and uniformity by achieving homogeneous integration of antiviral agents within alginate and chitosan matrices to ensure consistent antiviral effects while preserving mechanical and biocompatibility properties.
3. Viral testing and safety assessment by conducting rigorous antiviral assays, while ensuring the developed materials are non-toxic and safe for biomedical applications.
4. Optimization of material properties by balancing antiviral efficacy with essential properties such as biodegradability, mechanical strength, biocompatibility, and processability to meet the diverse needs of biomedical applications.

Methods Chosen to Address Challenges

1. Extraction and characterization of marine bacterial cultures will be subjected to optimized extraction protocols, and bioactive metabolites will be characterized using analytical techniques such as HPLC, mass spectrometry, and NMR spectroscopy.
2. Material synthesis of the extracted metabolites will be incorporated into alginate and chitosan matrices through methods such as solvent casting, crosslinking, and freeze-drying techniques to produce homogenous composites with controlled release properties.

3. Antiviral assays to determine the antiviral efficacy by using the double-layer method.
4. Physicochemical and mechanical characterization by TGA, DSC and FTIR spectroscopy, FESEM, mechanical testing, and biodegradability assays will be used to characterize the developed materials.
5. Biocompatibility testing through cytotoxicity assays, following ISO-10993 standards on fibroblast L929 and keratinocyte HaCaT cells, to ensure they are safe for potential biomedical applications.
6. Mechanistic studies to explore interactions between viral particles and the bioactive metabolites within the materials, using molecular docking during the three months secondment with a non-academic actor (ProtoQSAR).

Expected Results

- Development of antiviral material by integrating marine-derived bioactive metabolites into alginate and chitosan matrices.
- Broad-spectrum antiviral activity against a range of viral pathogens, with the potential for use in a variety of biomedical applications.
- Production of biocompatible and functional materials with desirable mechanical, physicochemical, and biocompatibility properties suitable for biomedical applications.
- Insights into the molecular mechanisms of antiviral action, paving the way for the rational design of future antiviral materials.
- This project represents a pioneering effort to combine marine-derived bioactive compounds with biocompatible polymers, aiming to produce antiviral materials with broad applications in biomedicine. It holds promise to address unmet needs in combating viral infections through innovative and sustainable solutions.

Scientific alignment with EU-DOCs for SmUCS objectives

The PhD thesis project proposal aligns strongly with the EU-DOCs for SmUCS program's scientific objectives by addressing pressing global health challenges through the development of innovative, sustainable antiviral solutions. Specifically, this thesis contributes to the scientific orientations of the program in innovation in antiviral solutions by exploring and utilizing bioactive metabolites from marine bacteria to create antiviral materials. The project pushes the boundaries of current antiviral strategies, demonstrating a novel biotechnological approach in line with the program's emphasis on ground-breaking research. Besides, the integration of marine-derived metabolites with biodegradable, biocompatible polymers like alginate and chitosan supports the EU's goals of sustainability and the reduction of environmental impact. This is particularly relevant given the EU-DOCs emphasis on environmentally conscious innovation, advancing materials that are not only effective but also ecologically friendly. The thesis focuses on combating viral infections, which aligns with SmUCS objectives to improve public health outcomes through scientific advancements. The development of materials capable of preventing viral infections has wide-ranging applications in healthcare, supporting safer and more effective medical solutions. This project bridges microbiology, material science, chemistry, and biomedical engineering, fostering an interdisciplinary approach that resonates with the EU-DOCs' mission to encourage collaborative and cross-sectoral scientific endeavours. By contributing to the development of next-generation antiviral materials with sustainable and innovative methodologies, this research directly supports the EU-DOCs objectives, offering potential for significant scientific, societal, and environmental impact.

Societal and economic challenges and contributions

Societal Challenges and Contributions

Viral infections pose a continuous global threat to public health, exacerbating healthcare burdens, and affecting millions of lives worldwide. This PhD thesis addresses the societal need for innovative and effective antiviral solutions by developing bioactive materials capable of preventing and mitigating viral transmission and infection, thereby contributing to global health security. By creating antiviral materials that can be used in biomedical applications such as protective coatings for medical devices, wound dressings and infection prevention clothing. This research has the potential to reduce the spread of viruses in clinical settings and beyond. This would lead to lower healthcare costs, improved patient outcomes, and enhanced public health resilience to viral outbreaks. This thesis aligns with growing societal demands for sustainable and eco-friendly innovations by using marine-derived bioactive metabolites combined with biodegradable polymers like alginate and chitosan. Reducing dependence on synthetic chemical treatments and creating biodegradable antiviral solutions supports

environmental sustainability and addresses pollution concerns linked to conventional antiviral products. The project fosters collaboration between fields such as microbiology, material science, biomedical engineering, and marine biotechnology, promoting knowledge exchange and cross-sectoral innovation that strengthens scientific capabilities and societal problem-solving potential.

Economic Challenges and Contributions

The development of effective antiviral materials can contribute to reducing healthcare costs by lowering infection rates, decreasing hospital stays, and minimizing the need for expensive antiviral medications or treatments. This offers economic benefits to healthcare systems and society at large. By utilizing bioactive compounds derived from marine bacteria, the thesis supports the growth of the bioeconomy, contributing to sectors focused on sustainable resource utilization and innovative bioproducts. This approach fosters economic growth within emerging markets tied to marine biotechnology and bio-based industries. The project has the potential to lead to the creation of marketable antiviral biomedical products, including coatings for medical devices, antiviral dressings, and other materials. This opens new avenues for commercialization, stimulating economic growth and creating jobs within the biotechnology and biomedical sectors. By leveraging marine biotechnology and developing high-value, sustainable materials, the thesis supports EU industries' competitiveness in the global market for antiviral and antimicrobial technologies. This aligns with European goals for innovation and leadership in health and biotechnology.

In summary, this PhD thesis addresses critical societal needs for effective antiviral solutions, while contributing economically by reducing healthcare costs, fostering sustainable industry growth, and creating innovative market opportunities. Its focus on sustainable, bio-based materials positions it to have a positive and lasting societal and economic impact.

Partnership context

The proposed PhD thesis project brings together a strong partnership between key research institutions and stakeholders to ensure a multidisciplinary and impactful research environment. The primary partners involved are the Catholic University of Valencia (UCV) and La Rochelle University, which provide complementary expertise and state-of-the-art facilities. UCV, led by a professor with extensive experience in antimicrobial biomaterials, contributes strong capabilities in chemical engineering, material development, and characterization, while La Rochelle University, led by a researcher specializing in microbial biology, offers critical expertise in biological evaluation and microbial characterization. This collaboration extends to the 4-year European MSCA Staff Exchange project "AQUAPACK" reflecting a history of successful cooperative research and knowledge transfer. Additionally, the PhD student will benefit from a 3-month secondment with ProtoQSAR, a company specializing in molecular modelling and drug design. This secondment will significantly contribute to the development and validation of antiviral materials. Both universities and ProtoQSAR are committed to providing high-quality training and mentoring to the PhD candidate. The laboratories are supported through internal and national grants, ensuring financial resources for research activities, technology transfer initiatives, and dissemination efforts. This partnership is further strengthened by connections to socio-economic and innovation-focused stakeholders, enhancing the relevance and application potential of the antiviral materials developed.