PhD candidate position (3 years)

Title : Viral Protease-assisted Combined Antiviral Therapy with photoactive "Lock and Release" supramolecular-antiviral-dots

Job type: 3-years PhD thesis (LUE contract, https://univ-lorraine/lue)

Period: from 01/10/2023 to 30/09/2026

Monthly gross salary: C.a. 2 300 €

Location : Laboratoire Lorrain de Chimie Moléculaire L2CM (http://www.l2cm.univ-lorraine.fr) Nancy - Grand Est – France.

Keywords: organic synthesis; antiviral molecules; coronavirus; virology; medicinal chemistry; chemical biology

Presentation of the host laboratory

The main laboratory for the PhD will be L2CM, which is a mixed research unit (UMR CNRS 7053) between University of Lorraine and CNRS (centre national de la recherche scientifique) located in Vandoeuvre-lés-Nancy. The objective of the L2CM is to develop methods for the synthesis of innovative molecules and molecular materials with applications in physics (catalysis, energy, luminescence) and biology (antibacterials, drug delivery, imaging).

Address

L2CM, Faculté des sciences et technologies, Rue du jardin botanique, 54506 Vandoeuvre-lés-Nancy, France

Context of the PhD research

Human coronaviruses (HCoV) are enveloped RNA viruses associated with mild to severe respiratory infections in humans, such as colds and pneumonia. To date, there are no specific approved treatments for these HCoV infections. Thus, the development of anti-HCoV agents therefore remains a public health emergency. The objective of the VIPRO-COMBAT project is to synthesize photoactive supramolecular antiviral dots (SAD) assemblies, unique as an "intelligent" prodrug delivery system, allowing site-specific activation by the viral protease, thanks to attaching a peptide sequence to a virus inhibitor, such as an antimicrobial peptide. A "Lock and Release" system will ensure the controlled activation of the prodrugs, which are then activated by near-infrared light radiation at the level of the infected tissues. This will guarantee a functional and controlled multimodal antiviral approach, combining the advantages of optical and acoustic imaging based on the study of vibrations induced in matter by light. Another objective of the study will be to elucidate the interaction of SAD with the target cell by transcriptomic analysis, but also the impact of the treatment on the immune response and on the phenomena of inflammation. The project is therefore a proof of concept for the use of anti-

infective prodrugs activated by a viral protease, associated with a fluorescence bio-imaging system and phototherapy.

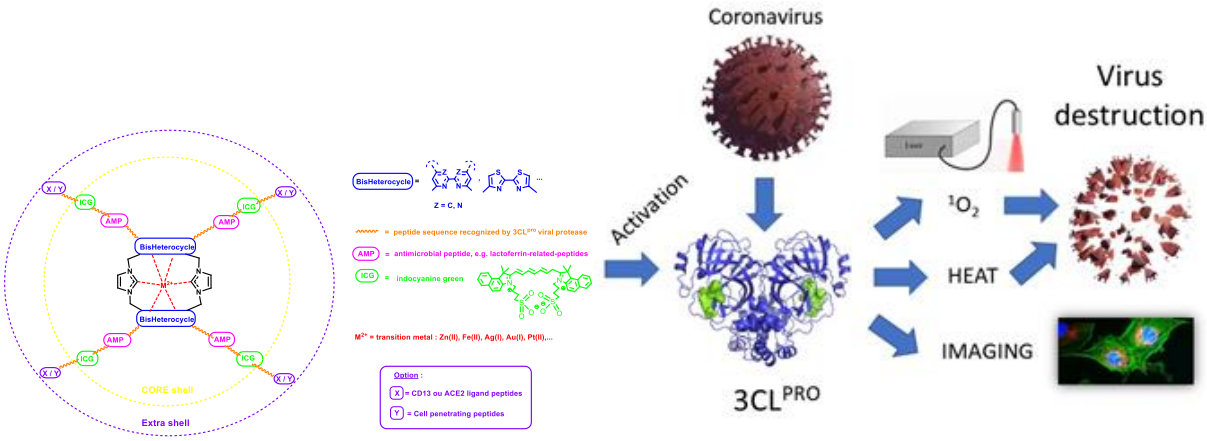

Figure 1. *Supramolecular-antiviral-dots (SAD) as smart prodrug delivery system*

Research methodology: The candidate will develop unique supramolecular-antiviral-dots (SAD) as smart prodrug delivery system (Fig. 1), activated specifically at the infection site by a viral protease, thus reducing the side effects and the systemic toxicity. The SAD will allow the construction of a "Lock and Release" structure that is suitable for specifically (1) producing a fluorescence signal in the target cells, (2) delivering antimicrobial peptides, (3) photoreleasing cytotoxic species ($^1O_2$) and increasing the temperature in the infected cell in a synergistic bimodal therapy, and (4) allowing photoacoustic (PA) bioimaging in the target tissues for medical diagnostics, a non-invasive sensing technique already used for biomedical applications. The "Lock and Release" system will ensure the specific activation of the multi-target prodrug only in the virus-infected cells and protecting the uninfected ones, in a controlled step-wise manner, where the final activation of the SAD can be visualized in cell and tissue imaging. These supramolecular-based antiviral and imaging agents can have a broad applicability in different emerging and re-emerging viral infections as a biocompatible phototherapeutic agent.

The PhD candidates will receive training in medicinal chemistry, drug synthesis, cell biology and virology.

Profile of the candidate

We look for a candidate holding (or near completion of) a Master's degree in Organic Chemistry, Pharmacy or similar, with competitive marks, eligible to apply for PhD fellowships. A background in organic synthesis, medicinal chemistry and/or chemical biology is highly recommended.

The PhD student will evolve in an environment composed of closely collaborating partner labs, such as CRAN (UL), RCSI (Dublin, Ireland) and LRGP (UL), with an international team composed of chemists, physicians, biologists, medical staff and pharmacists.

Supervisors of the PhD thesis

Dr Mihayl VARBANOV (Assistant professor, team MolSyBio, L2CM) - PhD co-Director (mihayl.varbanov@ univ-lorraine.fr). Phone: +33 03 72 74 73 19

Dr Florence DUMARCAY ((Assistant professor, team HeMaF, L2CM) - PhD Director (florence.dumarcay@univ-lorraine.fr). Phone: +33 372745665

Application deadline: 31st May 2023

Please send a CV, a motivation letter, the M1 and M2 marks and research experience to: mihayl.varbanov@univ-lorraine.fr and florence.dumarcay@univ-lorraine.fr

References

[1] Hannah Kunstek, Melaine Wang, Hiba Hussein , Ines Dhouib , Bassem Khemakhem , Arnaud Risler, Stephanie Philippot, Celine Frochot, Philippe Arnoux, Bertrand Fournier, MihaylVarbanov, Florence Dumarçay-Charbonnier. Synthesis, Photophysical Characterization and Evaluation of Biological Properties of C7, A Novel Symmetric Tetra-Imidazolium-Bis-Heterocycle. *Microorganisms* 2023, *11*(2), 495; doi : 10.3390/microorganisms11020495. ISI : 4,926

[2] Hannah Kunstek, Fanny Vreken, Aminata Keita, Michael R Hamblin, Florence Dumarçay, Mihayl Varbanov Pharmaceuticals. 2022, *15*(7), 858. Aspects of antiviral strategies based on different phototherapy approaches: hit by the light. *Pharmaceuticals* 2022, *15*(7), 858; DOI : 10.3390/ph15070858. Special Issue Photodynamic Therapy 2022. ISI : 5,215

[3] Hussein, H., Varbanov, M., Fournier, B., Dumarçay-Charbonnier F Tetrahedron. Lett. 2021, 79, 153288 Toward the synthesis of potential corono and clipcarbenes: new bis-imidazolium macrocycle and bis-imidazolium heterocycle ligands incorporating bis-bipyridine and bis-bithiazole units. DOI: 10.1016/j.tetlet.2021.153288. ISI : 2,032