PROGRAMME INTITUTS ET INITIATIVES

Appel à projet – campagne 2021

Proposition de projet de recherche doctoral (PRD)

MSTD - Maîtrise des syst tehno durables

Intitulé du projet de recherche doctoral (PRD): **ECOPHOTOSKIN**

Directeur.rice de thèse porteur.euse du projet (titulaire d'une HDR) :

NOM : **LEONARD** Prénom : **ESTELLE**
Titre : Choisissez un élément : ou Enseignant-chercheur
e-mail : estelle.leonard@utc.fr
Adresse professionnelle : ESCOM, 1 allée du réseau Jean-Marie Buckmaster, 60200 COMPIEGNE
(site, adresse, bât., bureau)

Unité de Recherche :
Intitulé : TIMR
Code *(ex. UMR xxxx)* : EA4297

École Doctorale de rattachement de l'équipe (future école doctorale du.de la doctorant.e) : **ED71 - Sciences pour l'ingénieur UTC**

Doctorant.e.s actuellement encadré.e.s par la.e directeur.rice de thèse (préciser le nombre de doctorant.e.s, leur année de 1e inscription et la quotité d'encadrement) : (1 doctorant, 2018, 50%)

Co-encadrant.e :

NOM : **VAYSSADE** Prénom : **MURIEL**
Titre : Professeur des Universités ou HDR ☒
e-mail : muriel.vayssade@utc.fr

Unité de Recherche :
Intitulé : BMBI
Code *(ex. UMR xxxx)* : UMR7338

École Doctorale de rattachement : **ED71 - Sciences pour l'ingénieur UTC**
Ou si ED non Alliance SU :

Doctorant.e.s actuellement encadré.e.s par la.e co-directeur.rice de thèse (préciser le nombre de doctorant.e.s, leur année de 1e inscription et la quotité d'encadrement) : 1 doctorant, 2018, 50% + 1 doctorant, 2018, 50% + 1 doctorante, 2019, 50%

Co-encadrant.e :

NOM : Prénom :
Titre : Choisissez un élément : ou HDR ☐
e-mail :

Unité de Recherche :
Intitulé :
Code *(ex. UMR xxxx)* :

École Doctorale de rattachement : **Choisissez un élément :**
Ou si ED non Alliance SU :

Doctorant.e.s actuellement encadré.e.s par la.e co-directeur.rice de thèse (préciser le nombre de doctorant.e.s, leur année de 1e inscription et la quotité d'encadrement) :

Cotutelle internationale : ☒ Non ☐ Oui, précisez Pays et Université :

Selon vous, ce projet est-il susceptible d'intéresser une autre Initiative ou un autre Institut ?
☒ Non ☐ Oui, précisez Choisissez l'institut ou l'initiative :

Description du projet de recherche doctoral *(en français ou en anglais) :*

Ce texte sera diffusé en ligne : il ne doit pas excéder 3 pages et est écrit en interligne simple.

Détailler le contexte, l'objectif scientifique, la justification de l'approche scientifique ainsi que l'adéquation à l'initiative/l'Institut.

Le cas échéant, préciser le rôle de chaque encadrant ainsi que les compétences scientifiques apportées. Indiquer les publications/productions des encadrants en lien avec le projet.
Préciser le profil d'étudiant(e) recherché.

1. Context, objectives and scientific approach.

Photopharmacology is an emerging approach based on light irradiation, which induced conformational changes in photochromic molecules and subsequently modify their biological activities. The spaciotemporal control, reversibility and versatility of photopharmacology was already applied for various health applications as for example the control of microtubule depolymerisation and cell death, the driving of neurotransmission, the modulation of GPRC protein family or even the release of antibiotics (Hauwert et al. 2018, Leippe et al. 2019, Li et al. 2018, Lichtenegger et al. 2018, Sailer et al. 2019, Velema et al. 2014). Thus the interest of photopharmacology for human health was stated and seems promising for the development of antibiotics, even if its potential is largely under-studied (Hüll et al. 2018, Leippe et al. 2017, Morstein et al. 2019).

Hence, the aim of ECOPHOTOSKIN project is to go further and assess the potential of photopharmacology to treat human skin disease and to tackle antibiotic resistance by combining five complementary aspects:

a) Covalently link known antibiotics to pharmacophores and test the physicochemical properties compared to unlinked azobenzenes ; b) Test the antibacterial properties on Class 1 bacteria ; c) Assess the safety of the molecules for the human skin and prove their efficiency on bacteria colonizing skin ; d) Evaluate the environment impact and degradation of the molecules ; e) Increase the social and cultural awareness of people on antibiotics misuse and environmental impacts

Firstly, photochromic compounds will be chosen based on preliminary results (Franche et al. 2020) with particular attention to the choice of the coupled antibiotic. Secondly, antibacterial activity will be evaluated on a panel of strains with and without irradiation to record its own effects. According to the studies of Lerch et al. 2016 we will focus on the skin infection application. It is noticeable that azobenzenic molecules have already been successfully tested against bacteria, including in our group (in example Franche et al. 2020, Ghoneim et al. 2018, Kaur et al. 2020, Piotto et al. 2017). However, few papers discussed the trans/cis isomerization impact on bacteria as did Feringa's group (Velema et al. 2013) who also associated an azo-moiety and ciprofloxacin or trimethoprim (Velema et al. 2015, Wegener et al. 2017). These hybrid molecules exhibited light-dependent activity towards E. coli. Moreover, the modification of the photoswitch can tune the irradiation wavelength from 365 nm to 652 nm, giving a better penetration of tissue and less side-effects. These reports led us

embrace new opportunities for antibiotic photopharmacology and space for innovation.

Then, the harmlessness of light irradiation process (required for the activation of compounds) on human skin will be assessed on a reconstituted human epidermidis (RHE), showing multilayered stratified keratinocytes. We will analyze the irradiation impact on the homeostasis of the tissue: i) cell proliferation (restricted to the basal layer of the epidermis) will be quantified ; ii) apoptosis (restricted to the stratum corneum) will be quantified using TUNEL assay; iii) skin irritation will be evaluated by measuring IL-1alpha release (ELISA assay), according to the OECD n° 439 guideline (2019). To assess the safety of antibacterial compounds on human skin and to better understand their biological effects, RHE models will be treated with molecules: morphology, proliferation, viability and irritation of the tissues will be quantified using the methods described above. In the last step, based on all results, the efficacy of compounds to treat skin infection model bacteria will be performed with and without light irradiation. Data obtained will bring knowledge about the modifications of the interactions between bacteria and human tissues during the treatment.

Moreover, experiments will be conducted with the help of a Master 2 student (not asked in this call of proposal) to monitor and anticipate the evolution of such drugs and to avoid the emergence of resistant bacterial strains by the molecules dissemination in the environment (Barnosky et al. 2012, The Lancet, 2012). Their impact on commensal soil strains, and biodegradation will be measured. In that context, photochromic moiety is expected to be a clear add-value.

Finally, to increase the social and cultural awareness of people on antibiotics misuse and environmental impacts, all along the thesis, posters and presentations will be done by the team for example during the “Fête de la science” event, and could lead to a more specific study by our partners in Lille.

Globally, the complementarity and expertise of each partners undoubtedly guarantee a successful outcome for our work.

References (in alphabetic order) :

A. D. Barnosky et al. Nature, 2012, 486, 52–58 ; A. Franche et al. Bioorg. Chem., 2020, 94, 103399 ; A. Ghoneim and N. M. Morsy, J. Iran. Chem. Soc, 2018, 15, 2567–2572 ; N. J. Hauwert et al. J. Am. Chem. Soc., 2018, 140, 4232–4243 ; K. Hüll et al. Chem. Rev., 2018, 118, 10710–10747 ; H. Kaur et al. Arab. J. Chem., 2020, 13, 377–392 ; P. Leippe et al. Biochemistry, 2017, 56, 5214–5220 ; P. Leippe and J. A. Frank, Curr. Opin. Struct. Biol., 2019, 57, 23–30 ; Z. Li et al. Org. Biomol. Chem., 2018, 16, 6988–6997 ; M. Lichtenegger et al. Nature Chem. Biol., 2018, 14, 396–404 ; J. Morstein and D. Trauner, Curr. Opin. Chem. Biol., 2019, 50, 145–151 ; S. Piotto et al. Molecules, 2017, 22, 1372 ; A. Sailer et al. Chembiochem, 2019, 20, 1305–1314 ; The Lancet, 2012, 379, 2117 ; W. A. Velema et al. Nat. Chem., 2013, 5, 924–928 ; W. A. Velema et al. J. Am. Chem. Soc., 2014, 136, 2178–2191 ; W. A. Velema et al. Bioconjugate Chem., 2015, 26, 2592–2597 ; M. Wegener et al. J. Am. Chem. Soc., 2017, 139, 17979–17986

2. Initiative « Maîtrise des systèmes technologiques sûrs et durables » MSTD and ECOPHOTOSKIN matching.

The Initiative aims to build and lead a community around research on man-made systems for his own use, which is the main objective of ECOPHOTOSKIN, as the enabling of antimicrobial activity by using light trend to make the antibacterial process safer, and as its sutainability testing is included in the project. Indeed, social acceptability, but above all respect for the environment and people are at the heart of the project. The transdisciplinary approches (chemistry, physicochemistry, bacteriology, cell and tissue biology, …) are clearly needed for its development. ECOPHOTOSKIN project will allow Muriel Vayssade and Estelle Léonard to merge for the first time their scientific skills to propose a new way for treating skin, based on a new technology. The project will also reinforce the

collaboration between TIMR and BMBI labs.

3. Contribution of each supervisor, brief timeline of the thesis, and previous achievements.

The first year of the thesis will consist in the preparation of the molecule candidate linking photochromic molecules and antibiotics, under the supervision of Estelle Léonard (TIMR), and with the collaboration of Junia in Lille. The second and third year of PhD will be dedicated to the physicochemical and antimicrobial tests as well as the skin tests under the supervision of the two PhD Directors Estelle Léonard (TIMR) and Muriel Vayssade (BMBI) in Compiègne (UTC). After having consequent data, Antoine Fayeulle (TIMR) will assess the environmental issue. Time will also be dedicated to the manuscript preparation, and the thesis defense.

4. Student profile

The student holding a Master 2 degree will have a strong background in biology, microbiology. A good knowledge of organic chemistry would be appreciated.

Main publications related to the project.

Franche, A. ; Pezron, I. ; Billamboz, M. ; Fayeulle, A. ; Deleu, M.; Léonard, E. Bioorg. Chem., 2020, 94, 103399. Amphiphilic azobenzenes: antibacterial activities and biophysical investigation of their interaction with bacterial membrane lipids.

Franche, A.; Imbs, C.; Fayeulle, A.; Billamboz, M.; Léonard, E. Chinese Chem. Lett., 2020, 31, 706-710. Zinc-mediated reactions on salicylaldehyde for Botrytis cinerea control.

Bois R, Abdellahi B, Mika B, Golonu S, Vigneron P, Chagnault V, Drelich A, Pourceau G, Wadouachi A, Vayssade M, Pezron I, Nesterenko A. Physicochemical, foaming and biological properties of lowly irritant anionic sugar-based surfactants. Colloids and Surfaces A: Physicochemical and Engineering Aspects. 2020. https://doi.org/10.1016/j.colsurfa.2020.125525.

Morales D, Lombart F, Truchot A, Maire P, Hussein M, Hamitou W, Vigneron P, Galmiche A, Lok C, Vayssade M. 3D co-culture models underline metastatic melanoma cell sensitivity to vemurafenib. Tissue Engineering Part A. 25: 1116-1126, 2019. doi: 10.1089/ten.TEA.2018.0210.

Lu B, Miao Y, Vigneron P, Chagnault V, Grand E, Wadouachi A, Postel D, Pezron I, Egles C, Vayssade M. Measurement of cytotoxicity and irritancy potential of sugar-based surfactants on skin-related 3D models. Toxicology In Vitro. 40 : 305-312, 2017. do

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Fichier envoyer simultanément par e-mail à l'ED de rattachement et au programme :
cd_instituts_et_initiatives@listes.upmc.fr avant le 20 février.