SORBONNE UNIVERSITÉ

CHINA SCHOLARSHIP COUNCIL

Appel à projets
Campagne 2022
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Title of the research project :

Deciphering the metabolic functions of two commensal polychaetes gut microbiota in the biosynthesis of nebulosins

Thesis supervisor (HDR) :

Name : HUBAS Surname : Cédric

Title : Dr

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Professional adress :
(site, dresse, bulding, office…) Station Marine de Concarneau, Place de la croix, 29900, Concarneau

Research Unit

Name : Biologie des Organismes et Ecosystèmes Aquatiques (BOREA)

Code *(ex. UMR xxxx)* :
UMR 8067

Doctorate School

Thesis supervisor's doctorate school (candidate's futur doctoral school) : ED227

PhD student currently supervised by the thesis supervisor (number, year of the first inscription) :

NA

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Joint supervisor :

Name : CALABRO Surname : Kevin

Title : Dr

email : kevin.calabro@mnhn.fr

Professional adress :
(site, dresse, bulding, office…) Fungi and Bacterial Natural Product Chemistry (CPNFB), 63 rue Buffon, 75005 Paris, France

Research Unit

Name : Molécules de Communication et Adaption des Micro-organismes (MCAM)

Code *(ex. UMR xxxx)* :
UMR 7245

École doctorale

Joint supervisor's doctorate school : Or, if non SU :
ED227

PhD student currently supervised by the joint supervisor (number, year of the first inscription) :
NA

Joint supervisor :

Name : Surname :

Title :

email :

Professional adress :
(site, dresse, bulding, office…)

Research Unit

Name :

Code *(ex. UMR xxxx)* :

École doctorale

Joint supervisor's doctorate school : Or, if non SU :

PhD student currently supervised by the joint supervisor (number, year of the first inscription) :

1) Study context

Marine annelids represent a perfect example of keystone species that maintain constant chemical interactions with bacteria, fungi but also with other invertebrates, to such extent that annelids harbor in their tissues symbiotic microbes that can yield metabolic responses such as defense strategies.

Microbial symbiont is well known to influence practically all aspects of eukaryote biology. However, our understanding of metabolic interactions between animals and their symbionts is limited. This is the case with annelids in which the role of their secondary metabolites involved in the chemical interactions between the host and its associated organisms remains unsolved.

A recent campaign of marine bioprospection of the Irish coastal areas initiated by our group lead to the isolation and characterization of a novel family of natural products isolated from the marine polychaete *Eupolymnia nebulosa*.[1] These metabolites named nebulosins, consist in a cysteine amino acid condensed on a tetraketide unit forming a rare and highly branched thiolane ring. Newsworthy, they are the first metabolites reported from this well-studied species.

Eupolymnia nebulosa is a widely spread terebellid worm usually living buried in tube-shape sand structures yet there is an increasing number of reports of it being enrolled in a host-symbiont association with sponges and other polychaetes such as the polynoid *Harmothoe areolata*. Even if toxic and deterrent properties have been proposed for *E. nebulosa* as anti-predatory strategies, no secondary metabolite has been correlated to this reported behavior so far.[2]

Nebulosins could potentially be responsible of the reported activity of *E. nebulosa*. Nebulosins contain structural features that suggest a possible microbial origin, namely a D amino acid (D-cysteine) and a mixed polyketide-amino acid pathway.

Moreover, in later sampling campaigns, *E. nebulosa* has often been seen living with another polychaete *Polynoe scolopendrina* sharing the same tube-shape sand structures. A UPLC-HRMS analysis of this worm extract evidenced the presence of nebulosins highlighting the strong ecological role of these compounds in this ecosystem. Metabolite transfer is quite rare in the marine environment with the exception of marine mollusks such as nudibranchs feeding on chemically rich sponges.

Deciphering the metabolic function of both polychaete microbiota is of great importance for a better and complete understanding of the ecological interactions observed in this coastal ecosystem.

2) Details of the proposal

The main objective of this proposal will be to identify the nebulosins producer by studying the metabolisation of labeled precursors in the gut of the both commensal worms. Through this project, few scientific questions will be answered: 1) Is the gut the area where nebulosins are concentrated? 2) What is

the role of nebulosins in the tripartite system (annelid/annelid/shared microbiota)? and 3) Is the nebulosin-producing symbiont able to biosynthesize these metabolites without any input from the host ?

In the course of its PhD, the successful candidate will first apply a metagenomics approach to compare the gut microbiota of both polychaetes.

Then, using a correlative imaging workflow including micro-computed X-ray tomography, nanoSIMS and FISH, the candidate will connect the metabolisation of nebulosins with the organ-scale and cellular three-dimensional distributions of microorganisms in the same host animal.[3] Prior the nanoSIMS analysis, the candidate will perform feeding experiments with selected labeled precursors of nebulosins, namely ^{15}N-L-cysteine, ^{34}S-L-cysteine, 3,3-D_2-L-cysteine and 1,2-^{13}C-acetate. An area enriched with ^{13}C and either ^{15}N, ^{34}S or ^{2}H, will be significant of the presence of nebulosins.[4,5] The EL-FISH imaging will allow the determination of the nebulosins producers in the targeted area.

Within an OSMAC strategy, the candidate will then chemically screen each isolated microbial strain in the targeted area for the production of nebulosins but also for the discovery of new natural products using a Molecular Networking approach (at MCAM).

Finally, the candidate will also assess the ecological role of these compounds including nebulosins through developed aquarium experiments in order to determine which family of compounds is responsible of the reported deterrent activity of *Eupolymnia nebulosa*.

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The SOMAQUA team (BOREA unit of MNHN, Concarneau Marine Station) possess all the facilities to perform both chemical ecology and stable isotope probing studies with state-of-the-art culture systems such as fully equipped aquaria, mesocosms and a seawater pumping system.

The CPNFB team (MCAM unit of MNHN) is particularly well-equipped to undertake the natural product chemistry aspect of the project. The laboratory has access to two NMR spectrometers (400/600 MHz cryoprobe), two LC-ESI-QTOF mass spectrometers as well as common analytical laboratory instruments (polarimeter, electronic circular dichroism, preparative and analytical HPLC). The laboratory includes a fungal and a bacterial culture service (incubators).

First year:

a) Culture of polychaetes and metagenomics
b) Feeding experiments with labeled precursors to confirm the biosynthesis of nebulosins.
c) Stable isotope experiments with the selected precursors on polychaete replicates.
d) Micro-computed X-ray tomography of transversal gut sections of the polychaete.
e) Writing at least one article. Present one poster in a conference.

Second year:

a) EL-FISH/nanoSIMS analysis of the gut micro-sections and correlations of imaging data.
b) Chemical screening of all cultured strains using a Molecular Networking approach. Isolation and structure elucidation (NMR spectroscopy and mass spectrometry) of the secondary metabolites.
c) Preparation of the aquarium experiments for the ecological study.
d) Writing at least one publication. Present one oral communication in a conference.

Third year:

a) Aquarium experiments and subsequent data treatment.
b) Writing the PhD thesis and writing article(s).

3) References

1. K. Calabro, L. K. Jennings, P. Lasserre, R. Doohan, D. Rodrigues, F. Reyes, C. Ramos and O. P. Thomas, *The Journal of Organic Chemistry*, 2020, **85**, 14026-14041.

2. D. Martin, C. Nourichel, M. Uriz, M. Bhaud and J.-C. Duchêne, *Bulletin of Marine Science -Miami-*, 2000, **67**, 287-298.

3. B. Geier, J. Oetjen, B. Ruthensteiner, M. Polikarpov, H. R. Gruber-Vodicka and M. Liebeke, *Proceedings of the National Academy of Sciences*, 2021, **118**, e2023773118.

4. C. Hubas, D. Boeuf, B. Jesus, N. Thiney, Y. Bozec and C. Jeanthon, *Frontiers in Microbiology*, 2017, **8**.

5. S. Cruz, C. LeKieffre, P. Cartaxana, C. Hubas, N. Thiney, S. Jakobsen, S. Escrig, B. Jesus, M. Kühl, R. Calado and A. Meibom, *Scientific Reports*, 2020, **10**, 10548.

4°) Profile of the Applicant (skills/diploma…)

The applicant should have knowledge and/or experience in:

- Natural product chemistry: isolation and structure elucidation using mass spectrometry and NMR spectroscopy
- Culture of marine fungi and bacteria
- Biosynthesis of natural products
- Metagenomics
- Chemical ecology

The applicant should have a first publication record expressing its ability to write scientific publications and a good command of scientific English.

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CALENDRIER DE LA CAMPAGNE

26 juillet
Lancement de la campagne
Diffusion de l'appel à projets par les écoles doctorales auprès de leurs encadrantes et encadrants.

Jusqu'au 17 septembre
Les chercheurs/enseignants-chercheurs et chercheuses/enseignantes-chercheuses de Sorbonne Université soumettent des propositions de projets de recherche doctoraux à leur directeur et directrice d'école doctorale (en utilisant le formulaire joint) et à l'adresse suivante : **https://inscriptions.sorbonne-universite.fr/lime25/index.php/344242?lang=fr**

Jusqu'au 24 septembre
Les écoles doctorales valident le cas échéant les projets et notifie le collège doctoral de leur décision à l'adresse suivante : **csc-su@listes.upmc.fr**

1er octobre
Mise en ligne des projets validés sur le site web de Sorbonne Université et ouverture des candidatures
https://www.sorbonne-universite.fr
Les candidats chinois prennent contact avec les porteurs et porteuses de projets et leur envoient un dossier de candidature.
Les candidates et les candidats déposent leur dossier à l'adresse suivante :
https://inscriptions.sorbonne-universite.fr/lime25/index.php/383154?newtest=Y&lang=fr

31 janvier
Fermeture des candidatures
Les porteurs et porteuses de projet ont transmis la candidature retenue après audition des candidates et candidats à leur école doctorale

Jusqu'au 21 février
Après examen, les écoles doctorales envoient les lettres de pré-admission signées et tamponnées des candidats et candidates retenues au collège doctoral

28 février
Le collège doctoral envoie les lettres de pré-admission aux candidates et candidats

Jusqu'au 31 mars
Les candidates et candidats retenus par Sorbonne Université candidate sur le site internet du CSC

31 mai
Diffusion des résultats par le CSC auprès de SU
Envoi résultats aux candidates et candidats ainsi qu'aux porteurs et porteuses de projet