Fungal Rational Induction of Natural Products

PhD in Bioinformatics in Nantes

Institutional Context

Within the ANR program FREE-NPs « Fungal Rational Induction of Natural Products » (https://unnews.univ-nantes.fr/...) of the ChiChaMVa (CHImiodiversité des CHAmpignons Marins et VAlorisations) team from the Mer, Molécules, Santé laboratory (MMS – EA2160 - https://mms.univ-nantes.fr/equipe-4-chichamva/), we are looking for a M2 student in bioinformatics. This project lead by MMS is also in collaboration with the ComBi team from LS2N (UMR CNRS 6004 – Laboratoire des Sciences du Numérique de Nantes) and the Dyliss team from IRISA in Rennes (Institut de Recherche en Informatique et Recherches Aléatoires).

Research Context

Nowadays, natural product research is still largely based on random screening of microbial extracts. This strategy is costly and time consuming and is one reason of the current decrease and mutation of natural product research in pharmaceutical companies [1]. This is even amplified in the case of microbial drug discovery as the general strategies consist in the culture of a large number of microorganisms in various culture conditions to produce as much chemical diversity as possible [2-4]. This project aims at developing rational approach to induce unprecedented microbial natural products from fungi as a model organism.

This PhD thesis proposes to use bioinformatics approaches, in combination with metabolomics [5, 6] and genomics [7-10], to rationalize induction strategies for NP production. This project is based on the analysis of fungal genome scale reconstructed metabolic network (GEM) [11, 12] to rationally select the appropriate culture conditions allowing increase in chemical diversity.

To achieve this goal, the key point lays in the use of accurate GEM that will be able to precisely predict compound production according to the culture conditions. The efficient completion of the GEM will be achieved using two different OMICS approaches. Genomic study of the strains will be used to reveal the hidden secondary metabolome present in both strain gene sequences [7-10]. Metabolomic strategy [6, 13], based on liquid chromatography coupled to high-resolution mass spectrometry, will be used to explore experimental compounds production by the two fungal strains during an OSMAC study (the One Strain Many Compound strategy consists in the growth of a microorganism in a large variety of culture media to provide a large chemical diversity) [14-16]. The latter result will provide: (1) after the deep dereplication of the chromatograms, a precise overview of the compounds produced by the two strains, and (2) information about metabolic regulation in the different culture media evaluated. All this information will clearly strengthen the GEM. Finally, the analysis of those Networks will yield the selection of novel culture conditions able to expand observable natural products for both fungal strains toward unprecedented chemical scaffold hidden in their genome.

This PhD Thesis aims at rationalizing the OSMAC approach to provide improved culture conditions with the consequence of reducing the duration and thus the cost of such study. This, so called "Smart" OSMAC approach, will be one key step forward toward the renewal of natural product drug discovery programs in pharmaceutical companies, as well as in academic institutions.

Student Profile

We are looking for a Master student in bioinformatics interested to work at the chemistry/biology interface with knowledge in System biology and network analysis.

Some knowledge in metabolomics and GEM reconstruction will be positively considered.

The PhD thesis will take place at MMS in Nantes, and some periods in Rennes should be envisaged.

The thesis will start in September/October 2019 with a founding already obtained for 3 years.

References

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