A comprehensive pipeline for the discovery of new bioactive marine natural products.

Several new marine natural products (MNPs) have been launched to the marketplace, and even more have entered preclinical and clinical trials. On the other hand, several issues hamper to fully leverage MNPs, such as the limited accessibility of marine sources, low yields, lack of data regarding the biological interacting targets, ethical concerns (impact on biodiversity). Cultivable marine microorganisms may be a way to circumvent these problems because: (1) many of the MNPs found in marine organisms are produced (or putatively produced) by microorganisms (2) many strains of marine microorganisms from all over the world are commercially available and can be purchase without any additional sampling on field, (3) the genomes of most of these strains have been sequences, and (4) the amounts of currently available of genomic data are by far larger compared to the capability of researchers to extract all the information they contain.

The discovery and exploitation of new bioactive MNPs will be pursued using an innovative strategy based on advanced bioinformatic and spectroscopic methods. Genome mining on available genome sequences of commercially available marine microorganisms will be used to hook biosynthetic gene clusters of pharmacologically active natural products, i.e., polyketides (PKs) and non-ribosomal peptides (NRPs). Microbial strains harboring biosynthetic gene clusters of interest will be purchased and talented microbes will be fermented in different conditions in order to trigger the production of encoded metabolites (OSMAC approach). The metabolic profile of the species under study will be studied through molecular networking (MN) based on LC-MS/MS data from their extracts. Structural determination will be achieved by extensive application of 1D/2D NMR spectroscopy and high-resolution MS2/MS3 spectrometry, and stereochemical issues will be solved through the combination of experimental methods (NMR and electronic circular dichroism, ECD) and quantum mechanical (QM)-based computational techniques. Finally, characterization of the pharmacological activity of the newly obtained compounds will be carried out, in collaboration with other research groups, through bioinformatic (Inverse Virtual Screening) and experimental approaches.