



# Bioprospecting of Uncultured Marine Microorganisms Needs More New Cultivation Techniques for Natural Products Discovery



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## Introduction

Natural products are benefit for human health such as using in organ transplantation, cancer treatment and cholesterol control as well as serving as antibiotics, insecticides, and antiparasitics<sup>[1]</sup>. More than 15,000 structurally diverse marine natural products (MNPs) have been discovered since the 1970s<sup>[2]</sup>, in which the major source is marine microorganism. However, to date, five phyla Actinobacteria, Bacteroidetes, Cyanobacteria, Firmicutes, and Proteobacteria that represent 95% of all cultivated and published species produce bioactive molecules<sup>[3]</sup>. The limited diversity of culturable microorganisms is thereby one of the most important reasons for the collapse of the antibiotic discovery pipeline that the last new class of antibiotics daptomycin discovered in 1987 has been successfully developed into a clinical therapeutic<sup>[4]</sup>. Hence, isolation and cultivation of new marine microorganisms especially uncultured microbes (do not grow under laboratory conditions) might be a shortcut to discover novel MNPs that is a perpetual need to combat new diseases and drug-resistant pathogens for public health<sup>[5, 6]</sup>.

However, approximately 99% of microbial species cannot be cultured by traditional techniques<sup>[6,7]</sup>. Because pure culture may be the only way to comprehensive characterization of physiological properties and full assessment of application potential of individual microbial species<sup>[8]</sup>, developing cultivation techniques play an important role for systematic investigation of uncultured marine microorganisms, there by allowing for the exploitation of the previously inaccessible MNPs. Therefore, a significant focus for marine microbiologists today is to develop strategies to cultivate the uncultured majority of the microbial world for MNPs discovery.

Despite some novel microbial species were successfully cultured by varying media and growth conditions, new technologies and cultivation approaches iChip<sup>[6]</sup>, high-throughput extinction culturing<sup>[9,10]</sup>, diffusion chamber<sup>[11]</sup>, single cell encapsulation combined with flow cytometry<sup>[12]</sup>, coculture<sup>[13]</sup>, microbial culture chip<sup>[14]</sup>, filtration-acclimatization<sup>[15]</sup>, double encapsulation<sup>[16]</sup>, micromanipulator<sup>[17]</sup>, optical tweezers<sup>[18]</sup>, transwell plates<sup>[19]</sup>, and community culture<sup>[20]</sup> have been emerged for culture of uncultured microorganisms. Although the above cultivation techniques have a significant effect on isolation of uncultivated microorganisms, novel approaches and techniques of isolation and cultivation will still be required for recovering more uncultivated microbial species to find the structurally unique MNPs with interesting biological activities. For instance, several promising techniques e.g., single cell Roman sorting<sup>[21]</sup> and micro fluidic system<sup>[22]</sup> could be developed for growing marine uncultured microorganisms.

Uncultured microorganisms have recently been reported to produce a new cell wall inhibitor teixobactin that kills pathogens without detectable resistance<sup>[6]</sup> and other diverse MNPs<sup>[23]</sup>, new technologies for bio-prospecting of marine uncultivated microbes thus have the great application potential for the discovery of MNPs with unique scaffolds and for exploitation in the pharmaceutical and agricultural industries. I believe new uncultivated marine microorganisms will be better understood and discovered in the next decade by a combination of both conventional and innovative approaches, which allow for the exploitation of MNPs potential as a source of drug discovery.



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