

## Previously Unexplored Bacteria as Promising Source in Drug Discovery in Future

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Secondary metabolites (SMs), usually synthesized by microorganism as the non-essential component in their metabolic process. They can be utilized as effective “drug leads” for the ailment of different disease conditions [1]. These SMs usually possess diverse pharmacophore with high structural, but still, there is a demand for novel NPs with better activities or the novel mechanism of action [2,3]. Hence, there is a growing interest in the precise screening of microbial flora, isolation and production of bioactive components from such microbes, and in cases structural modification based on structural activity relationship [4]. Generally, these approaches rely on pure culture or single isolate, more precisely culture dependent biochemical characterization and metabolite profiling.

Recently, there is interest in isolation of novel molecules from previously uncultivable or unculturable microorganisms in normal lab conditions. However, with tremendous hits and trial different novel bacterial species were successfully cultured by varying media and growth parameters [5]. The major breakthrough in this field has been by the introduction of novel cultivation methodologies such as the use of a diffusion chamber [6], or isolation chip (ichip) [7]. The diffusion chamber is designed to trick the cell by incubation in experimental setup mimicking their natural habitat [6]. The ichip contain the central plate for incubating the cells separated by a semipermeable membrane to restrict the cell movement. The ichip is incubated directly in the natural habitat or slightly altered settings than the original habitat [7]. The diffusion chamber has been successfully used for cultivation of bacteria, which were uncultivable, previously [8]. Similarly, ichip has been utilized for high-throughput in-situ cultivation of previously designated “uncultivable” microbial species [7]. The precise isolation of *Eleftheria terrae*, previously undescribed soil microorganism by ichip technology provided new avenues for exploring the novel secondary metabolites, Teixobactin [8]. Teixobactin has been classified as a new class of antibiotics with effective activity against Gram-positive bacteria by inhibiting peptidoglycan biosynthesis. More importantly, there was no report of teixobactin resistant bacterium [8,9]. These findings strongly support that the access to previously uncultured microbiota by developing effective isolation and cultivation can provide access to their biosynthetic machinery to derive novel biomolecule with novel bioactivities.

Another interesting approach for exploring the previously unexplored habitats such as exploring the microorganisms dwelling as commensals or in host-parasite relationship. Some of the interesting examples include isolation of antimicrobial molecule, lugdunin from human-associated bacteria *Staphylococcus lugdunensis*. Lugdunin is bactericidal against major pathogens and not prone to resistance to *S. aureus* [10]. Another example includes isolation and characterization of formicamycin, an effective antibacterial produced by *Streptomyces formicae* isolated from African *Tetraponera* plant-ants [11]. Thus, it is evident that the previously unexplored microbiota residing on the unusual habitats can provide effective bioactive molecules with the novel mode of actions.

Besides these culture dependent strategies, the culture-independent approaches as “metagenomics” has a high potential for getting access to novel and more effective drug molecules. The major constraint of culture-dependent approach is that not all microbes are cultivable in lab condition, and even if cultivated there is no guarantee that all the molecules are produced at a particular culture condition. The

approaches as metagenomics which is culture independent but precise, have tremendous potential to connect the genetic information directly to the production of bioactive molecules [12]. The isolation of malacidins as a promising new class of calcium-dependent antibiotics through soil metagenomics illustrates the tremendous potential of such culture independent strategies for drug discovery in days to come [13]. Similar to metagenomics, other approaches as “metatranscriptomics” “metaproteomics” and “metabolomics” are popular strategies for studying the physiology, genetics, and biochemistry of microbial communities [4]. The appropriate connection of these approaches in the drug discovery can open up new opportunities for isolation and development of novel and effective drugs.

In conclusion, the surge of promising drug leads has diverted from normal/easily cultivable microbiota to uncultivable microorganism or microbiota from unexpected habitats. In addition, the culture-independent approaches as metagenomics have revolutionized the arena of exploration of microbial-derived drug molecules. Moreover, the recent application of advanced biological and chemical approaches has tremendous opportunities to drive this area of drug discovery to new era [14].

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