

## Metagenomic-Guided Antibiotics Discovery

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The extensive emergence of multi-drug-resistance pathogens e.g., New Delhi metallo-beta-lactamase 1 (NMD-1) Gram-negative bacteria cause a huge threat to public health. One direct course of action to treat drug-resistant pathogenic infections and avoid an epidemic is to discover new antibiotics [1]. However, during the past 50 years of intensive screening, the pace of antibiotic discovery and development with unique scaffolds is dramatically declining. Since the already-discovered antibiotics are still high-frequency isolated and rapid dereplication techniques for antibiotics are still lacking, the major pharmaceutical companies have noticeably downsized their investment in antibiotic discovery, even stopped doing research in this area [2]. Accordingly, to meet the urgent demand for novel drug, a recent trend in antibiotic discovery from natural sources emphasizes the investigation of metagenomics.

Metagenomics enables direct access to the whole genome of the natural environment through the introduction of environmental DNA (eDNA) into a suitable host and screening of these large eDNA libraries [3]. Discovery of novel natural products (e.g., terragines, violacein, indirubin and turbomycins) with various bioactivities by metagenomic has proven that this method is a good tool for antibiotic discovery [4]. To date, function driven analysis (e.g., bioactivity assay) and sequence driven analysis (e.g., DNA probe screening) are two main strategies for eDNA library screening [3,5,6]. Sequence driven analysis could identify the large discrete DNA fragments for the assembly of the intact clusters [7]. Kim et al. [8] reported a general framework for the recovery of large functional DNA fragments from cosmid clones and efficient reassembly of these large fragments using transformation-associated recombination (TAR) in *Saccharomyces cerevisiae* according to sequence driven analysis. Feng et al. [9] used TAR method to reassemble two characterized eDNA clones (named AB649 and AB185) into a complete PKS cluster and heterologously expressed in *Streptomyces albus*. Three novel antibiotics fluostatin F, G and H with antibacterial activities were detected in the assembled clone, but not found in AB649 cultures alone [9].

The development of diverse model systems for eDNA libraries expression could also expand the repertoire of antibiotics. Despite

much attempts on eDNA expression in *E. coli*, Craig et al. [10] explored  $\beta$ -Proteobacterium *Ralstonia metallidurans* as a new model system for eDNA expression. Novel antibiotics such as patellamide and pederin were isolated by this new system [10]. Interestingly, cosmids conferred the production of novel antibiotics in *R. metallidurans* were not functioning in *E. coli*. Although the search for antibiotics by metagenomic methods has only just begun, it is no doubt that metagenomics is a productive source of novel secondary metabolites and has great potential to increase the number of antibiotics in clinical trials.

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