27O-ISMS12 **Natural Product Discovery by Heterologous Expression of Cryptic Biosynthetic Pathway in *Aspergillus oryzae***

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New chemical entities are crucial for discovering groundbreaking drug therapies and providing biological insight. Natural products and their semi-synthetic derivatives have played a prominent role in the history of drug discovery and remain the most attractive source of potential drugs and biological probes because of their structural complexity and diversity.

Filamentous fungi are well known for producing a variety of secondary metabolites, and many of these metabolites exhibit medicinally important properties. Therefore, constructing a diverse library based on fungal secondary metabolites would increase the likelihood of discovering new drug candidates. Fungal genome sequences demonstrate the presence of numerous transcriptionally suppressed biosynthetic pathways, and the bottomless capacity of fungal biosynthesis is expected to provide a wide range of novel secondary metabolites. However, most of the biosynthetic gene clusters are silent under normal culture conditions and a lot of natural products are remained to find. To access the cryptic natural products encoded by silent biosynthetic pathways, we applied post-genomic natural product discovery by combining genome mining and heterologous expression system of *Aspergillus oryzae*. One of our targets was fungal diterpenoid pyrones because of their unique structures and potent biological activities. We found five types of diterpenoid pyrone biosynthetic gene clusters in *Arthrinium*, *Metarhizium*, *Fusarium*, *Macrophomina* and *Colletotrichum* fungi by genome mining. Based on the genomic information, we reconstructed those biosynthetic gene clusters, and successfully not only obtained novel analogs but also unveiled their biosynthetic machinery. We further reorganization of the diterpene pyrone clusters to generate non-natural natural analogs. In this symposium, we show the methodology, results, problems and potential of the post genomic natural product discovery.