

## Innovative Strategies in Natural Products Science

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Natural products represent a vast structural diversity not matched by any other source of small molecules and they remain the best source and inspiration for the discovery of new drugs and molecular targets. Realization of the importance of the identification of new chemotypes for applications in health and agriculture led us to explore innovative strategies to exploit the full range of structural and functional diversity of small molecule natural products. Strategies we employ include the search for natural products from unconventional sources, discovery of their new uses, and application of innovative techniques for their structural diversification, and large-scale production of those with potential agricultural and medicinal applications.

The growing body of evidence suggests that symbiotic microorganisms represent a huge and a largely untapped resource of small molecule natural products with chemical structures that have been optimized by evolution for biological and/or ecological relevance (Gunatilaka, 2006). In our search for small molecule bioactive agents from symbiotic microorganisms and arid land plants, we have screened extracts derived from them in several functional assays including heat shock induction assay (HSIA) that targets heat shock response (Turbyville *et al.*, 2006; Falsey *et al.*, 2006; McLellan *et al.*, 2007) and inhibition of cell migration (Paranagama *et al.*, 2007a). Recent evidence in a wide range of model systems supports the pivotal role for the cellular heat shock response in helping cells cope with protein mis-folding. Thus, modulation of heat shock response should have implications in some diseases of the modern age (cancer, neurodegeneration, etc.) and stress tolerance of plants in arid land ecosystems.

The first part of this presentation will deal with discovery of some new uses for HSIA-active small molecule natural products from plants and symbiotic microorganisms and new approaches to enhance their production (Paranagama *et al.*, 2007b; Xu *et al.*, 2009). Our innovative strategies to enhance structural diversity of natural products involve a soil-less plant cultivation technique (Xu *et al.*, 2011), manipulation of fungal strains and their culture conditions to obtain "unnatural" natural products, and a chemical approach of converting carbonyl-containing natural products prevalent among fungal secondary metabolites into their analogs containing N-N moieties very rare in nature but common among "drug-like" combinatorial and synthetic molecules. Second half of this presentation will illustrate approaches used to enhance structural diversity of small molecule natural products.

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