

# *Abbott Workshop Series in Synthetic Organic and Medicinal Chemistry*

## **PROFESSOR DAVID SHERMAN**

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Research efforts over the past decade have evolved into several programs that are distinct in focus, yet coalesce into an overriding theme that include molecular genetic, biochemical and bioorganic chemical studies of microbial natural product biosynthesis.  
<http://www.lsi.umich.edu/facultyresearch/labs/sherman>



### *Novel Drug Leads from Natural Products and their Derivation from Microbial and Biosynthetic Diversity*

#### **Abstract:**

We have synthesized the natural pikromycin biosynthetic pathway pentaketide and hexaketide chain elongation intermediates as N-acetyl cysteamine (NAC) thioesters and employed them as substrates for in vitro conversions with engineered PikAIII-TE, and in combination with native PikAIII (module 5) and PikAIV (module 6) multifunctional polyketide synthases from *Streptomyces venezuelae*. These studies have demonstrated directly the remarkable ability of these monomodules to catalyze one or two chain extension reactions, keto group processing steps, acyl-ACP release and cyclization to generate 10-deoxymethynolide and narbonolide. Similarly efforts have now been completed with the corresponding erythromycin pentaketide chain elongation intermediate using the DEBS modules 5 and 6 multifunctional PKSs. This work has offered fresh insights into the flexibility of modular PKSs toward complex unnatural substrates for generation of novel natural product molecules. In addition, studies of the corresponding cytochrome P450 enzymes from these and related macrolide biosynthetic systems have shown their unique attributes as biocatalysts toward C-H bond activation against carbonyl substrates. During the past several years, we have expanded our analysis of microbial systems by investigating the cryptophycin biosynthetic pathway from *Nostoc* sp. ATCC 53789. In this work, we synthesized, purified and analyzed a series of synthetic linear chain elongation intermediates to develop a novel chemoenzymatic synthesis of the cryptophycin/arenastatin class of anti-tumor agents. This work has expanded to analysis of marine cyanobacteria that are extraordinarily rich in their production of biologically active and structurally unique natural products. Our studies provide a comparative biosynthetic case study of curacin A and jamaicamide, bioactive natural products isolated from the marine cyanobacterium, *Lyngbya majuscula* using genetic, biochemical and enzymatic approaches.

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## **4:15 p.m. Friday, May 20**

## **331 Smith Hall**

Host: Robert Fecik

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