We Are Pleased to Announce a Seminar Presented by:

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“Discovery and biosynthesis of highly modified peptidyl-nucleoside antibiotics from Actinomycetes”

Thursday, December 8, 2016 at 9:00 AM
Astellas Conference Room, SLSRC 3410/3430
Refreshments will be served at 8:45 AM

Natural products from microorganisms remain the single best source for drugs to treat infectious disease. Several new natural products have been discovered the past decade by using an activity-based screen to identify inhibitors of bacterial translocase I (UDP-N-acetylmuramic acid-pentapeptide:undecaprenyl phosphate transferase), an essential enzyme involved in the biosynthesis of peptidoglycan cell wall. An interesting feature of most of these potential antibiotics is that they structurally consist of unusually modified nucleoside cores that are likewise appended with unusual sugars, peptides, and polyketides/fatty acids. We have identified the biosynthetic gene clusters for several of these natural products including several capuramycin-type antibiotics, which are structurally characterized as peptidyl-sugar-nucleoside hybrids, and caprazamycin-type antibiotics, which are structurally characterized as hybrids of all the aforementioned components. We will present progress toward delineating the biosynthesis of these two groups of nucleoside antibiotics, highlighting the novel enzymatic strategies that have been discovered for diverting the canonical nucleoside into secondary metabolism, which includes reactions catalyzed by a non-heme, Fe(II)-dependent α-ketoglutarate:UMP dioxygenase and a pyridoxal-5’-phosphate-dependent L-Thr:uridine-5-aldehyde transaldolase. The discovery of these enzymes has enabled a genomics-guided approach to identify distinct yet structurally related nucleoside antibiotics. Additionally, we will discuss the enzymes required for piecing the antibiotic together by a convergent biosynthetic strategy, which includes several that have been exploited for structural diversification of the parent nucleoside antibiotic via chemoenzymatic and mutasynthetic approaches.

Bio: B.S. Molecular Biology, University of Wisconsin, Madison, WI, 1998; Ph.D. Chemistry (with Prof. Dirk Iwata-Reuyl), Department of Chemistry, Portland State University, Portland, OR, 2003 (mechanistic enzymology, protein characterization, tRNA modification); NIH-NCI Postdoctoral Research Fellowship (with Prof. Ben Shen), Department of Pharmaceutical Sciences and Department of Chemistry, School of Pharmacy, University of Wisconsin, Madison, WI, 2004-2007 (enzymology of enediyne biosynthesis, natural product biosynthesis, drug discovery); Assistant Professor, Department of Pharmaceutical Sciences, University of Kentucky, Lexington KY 2007-2013; Associate Professor, Department of Pharmaceutical Sciences, University of Kentucky, Lexington KY, 2013-present