Postdoc position in cofactor and natural product biosynthesis

Duke University School of Medicine, Department of Biochemistry, Yokoyama Lab

NIH-funded postdoc positions are available in Kenichi Yokoyama's lab (https://sites.duke.edu/yokoyamalab/) for highly motivated new PhD scientists interested in studying biosynthesis of natural products and cofactors. Our group studies the biosynthesis and mechanism of action of natural products and cofactors and apply the knowledge to discover novel therapeutics. We use a combination of approaches from organic chemistry, biochemistry, molecular biology and biophysics with particular focus on in vitro functional and mechanistic characterization of enzymes, small molecule characterization, bacterial and fungal/yeast genetics, synthetic organic chemistry, NMR, EPR and fluorescence microscopy. We are seeking for highly motivated postdocs with strong background in synthetic organic chemistry or bio-organic chemistry. Duke University School of Medicine offers an outstanding training environment for postdoctoral scholars and a strong track-record of almni achievement in academic and industrial careers. To apply, please send a cover letter explaining your career goals and research interests, a CV and names of three references to ken.yoko@duke.edu. Please also feel free to contact with any questions.

Research focus: Understanding the mechanism of biosynthesis and action of natural products is important for their future development into novel therapeutics. Overall goal of our lab is to provide comprehensive understanding about the biosynthesis and mechanism of action of natural products and cofactors. Particularly, we focus on natural products whose biosynthesis requires free radical mediated reactions represented by radical SAM enzymes (Fig. 1). To this end, we combine (1) functional and mechanistic enzymology, (2) structural biology, (3) genome mining, and (4) gene knockout experiments.

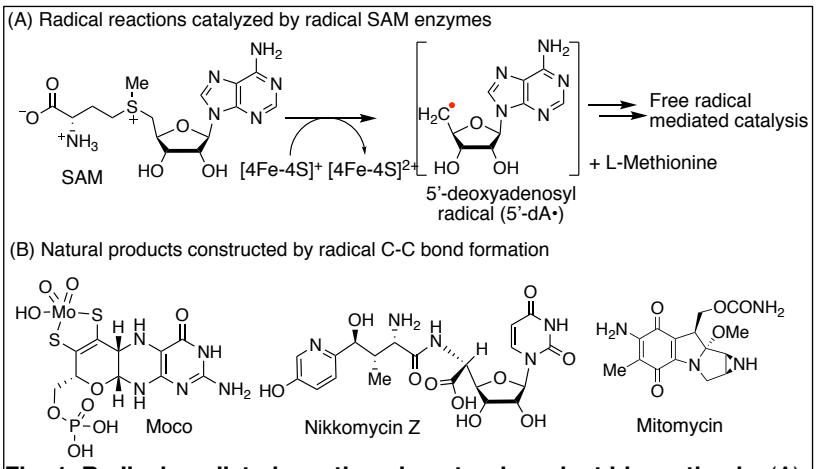

Fig. 1. Radical mediated reactions in natural product biosynthesis. (A) Common reaction catalyzed by radical SAM enzymes. (B) Examples of natural products that we study biosynthesis.

For example, one of our foci is the molybdenum cofactor (Moco, Fig. 2) biosynthesis. Moco plays key roles in chronic bacterial infection and human inheritable disease (Moco deficiency). We recently discovered a novel and cryptic biosynthetic intermediate 3',8-cH$_2$GTP, and revealed the functions of two enzymes, MoaA and MoaC (Fig. 2; *JACS* **2013**, *135*, 7019-32; *PNAS* **2015**, *112*, 6347-52.). We are now characterizing the mechanisms of these enzymes with immediate focus on: (1) mechanistic enzymology using substrate analogs combined with biophysical spectroscopy, (2) enzymological and structural characterization of peptides that rescue the catalytic function of MoaA variants found in human Moco deficiency patients, (3) development of inhibitors against enzymes from bacterial pathogens. Recent example of our mechanistic studies can be found in *JACS* **2020**, *142*, 9314–9326. The project will be extended to humans and pathogenic bacteria.

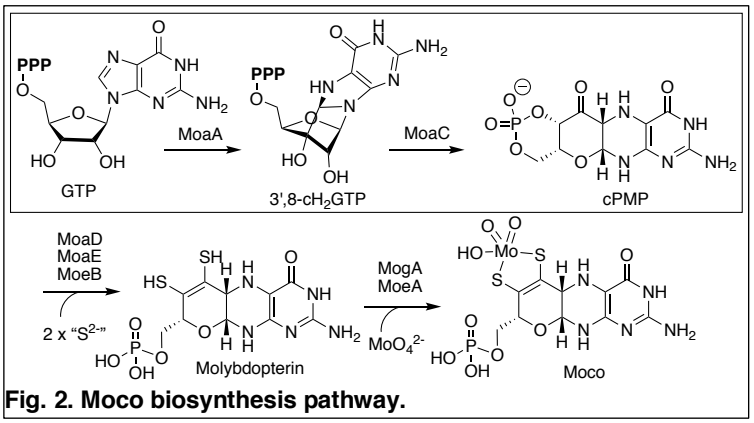

Fig. 2. Moco biosynthesis pathway.

Another example is antifungal nucleoside biosynthesis, in which we recently uncovered most of the steps required for nikkomycin Z biosynthesis (Fig. 1B, *Nature Chemical Biology* **2016**, 12, 905-907; *Nature Chemical Biology* **2020**, in press). We are currently performing structural and mechanistic characterization of biosynthetic enzymes and genome mining discovery of novel antifungal nucleoside natural products.

We also study the mechanism of action of the target natural products, in which biosynthetic understanding is used to provide novel molecules and our enzymology expertise is used to study the drug target. *Thus, postdocs in our group will obtain comprehensive research experience around the biochemistry of natural products.*