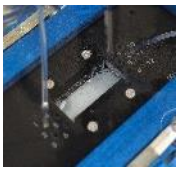
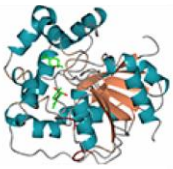
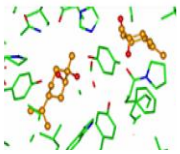
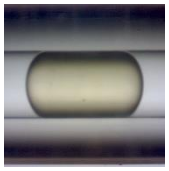

ESAB European Society of Applied Biocatalysis

ESAB Webinar

Biocatalytic Total Synthesis

December 16th 2022 **08.00-10.00 Eastern Standard Time (EST)**
13.00-15.00 Greenwich Mean Time (GMT)
14.00-16.00 Central European Time (CET)
20.00-22.00 China Standard Time (CST)
21.00-23.00 Japan Standard Time (JST)

Chairs: Jennifer Littlechild (University of Exeter)
Roland Wohlgemuth (Lodz University of Technology)

PROGRAMME

14.00 (CET) Prof. Dr. Sarah O'Connor, Director, Department of Natural Product Biosynthesis Max Planck Institute for Chemical Ecology, Hans-Knöll-Straße 8, 07745 Jena, Germany

Harnessing the chemistry of plant natural product biosynthesis

Plants, which make thousands of complex natural products, are outstanding chemists. Through the concerted action of enzymes that are assembled into metabolic pathways, nature creates enormous chemical complexity from simple starting materials. This talk will highlight the discovery process for enzymes that catalyze unusual or unprecedented enzymatic transformations, mechanistic and structural characterization of these enzymes, and methods by which these enzymes can be harnessed for metabolic engineering to generate pharmacological important compounds. A variety of different plants and molecules are used for these studies, most notably the monoterpene indole alkaloids and the monoterpenes known as iridoids.

14.30 (CET) Prof. Dr. Xiaoguang Lei, Department of Chemical Biology, College of Chemistry and Molecular Engineering, Peking University (PKU), Beijing 100871, China

Intermolecular Diels-Alderases: Discovery and Applications in Natural Product Synthesis

The Diels-Alder reaction is one of the most powerful and widely used chemical transformations in organic synthesis to make thousands of natural products and drug molecules. Although the preeminence of Diels-Alder reactions in the biosynthesis of numerous natural products, few naturally occurring enzymes have been shown to catalyze intermolecular transformations to date. We have reported a standalone flavin adenine dinucleotide (FAD)-dependent enzyme, MaDA, identified from the Morus plant, which catalyzes an intermolecular [4+2] cycloaddition to afford natural product chalcomoracin. It is the first enzymatic example of the naturally occurring monofunctional and intermolecular [4+2] Diels-Alderase [1] (Gao et al, Nature Chemistry 2020, 12, 620). MaDA has been further applied to facilitate the chemoenzymatic total syntheses of artonin I [2] (Liu et al, Biotechnol. J. 2020, 15, 2000119). In addition, we have discovered the first intermolecular exo-selective Diels-Alderase in nature and have elucidated the origin of exo-selectivity for broad synthetic applications to make complex natural products, drugs, and functional molecules [3] (Gao et al, Nature Catalysis 2021, 4, 1059). Empowered these discoveries, we have accomplished the diversity-oriented synthesis of many natural product-like molecules by combining enzymatic intermolecular Diels-Alder reactions and decarboxylative functionalizations [4] (Wang et al, Chem Catalysis 2022, DOI: 10.1016/j.checat.2022.10.027).

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15.00 (CET) Prof. Jürgen Rohr, Ph.D., FRSC, College of Pharmacy, University of Kentucky, Lexington, KY, USA

Enzymatic Total Synthesis Approaches to Solve Enigmatic Biosynthetic Pathways and to Generate New Natural Product Analogues

Enzymes provide unique features that are attractive to solve chemo- and enantioselectivity problems in synthetic approaches, and enzymatic steps are occasionally used to overcome such problems. However, enzymes are not easily integrated into organic synthetic schemes, and require water solubility as well as co-factors and co-factor regeneration. Our laboratory used enzyme mixtures to interrogate biosynthetic pathway steps and to manipulate biosynthetic pathways towards new hybrid natural products. Interrogating glycosyltransferases requires the generation of complex nucleosyl-diphosphate sugars that are not easily acquired by chemical total synthesis. Various TDP (thymidine-diphosphate)-sugars were generated instead through enzyme mixtures [1,2]. Their encoding genes could also be assembled in plasmids that were used to manipulate sugar patterns of natural products, most successfully of aureolic acid anticancer antibiotics [3]. An enzyme mixture plug-and-play system generated to synthesize the defuco-gilvocarcin framework was essential to elucidate and assign the role of oxygenases that generate the molecular framework of the gilvocarcin-type antibiotics [4-6].

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15.30 (CET) Prof. Dr. David H. Sherman, University of Michigan, Life Sciences Institute, Departments of Medicinal Chemistry, Chemistry, Microbiology & Immunology, Ann Arbor, Michigan, USA

Biocatalysis in ring assembly and late-stage C-H functionalization of complex molecules

Bacterial modular polyketide synthases are multi-functional enzymes that mediate the assembly of structurally diverse natural products. Many of these metabolites have been developed into clinically approved antibiotics, anti-parasitic agents, and cancer therapeutics. Over 30 years, numerous groups have worked to understand the function and structural parameters involved in creating chemical diversity from modular PKSs through in vivo and in vitro approaches. Although some successes have been reported, there continues to be a need to dissect the role of individual catalytic domains, protein-protein interactions, and substrate selectivity parameters to engineer these systems. We have focused on studies of 12-, 14- and 16-membered macrolactone-generating PKSs to understand bottlenecks in production of new metabolites using unnatural chain elongation intermediates. A particular focus has been the PKS terminal thioesterase domain and the determinants that contribute to selectivity and macrolactonization. Recent studies have revealed the ability to maximize efficiency of macrolactone formation by appropriate pairing of a TE domain in an engineered PKS involved in processing of unnatural substrates. We have also significantly expanded our pool of unnatural substrates to assess flexibility of PKSs toward proximal/distal functional group alterations, heteroatom replacements, and odd-numbered chain elongation intermediates. In numerous examples, new 12-, 14- and 16-membered ring macrocycles are generated and can be further transformed into novel macrolides by glycosylation and late-stage oxidation with heterologous CYP450s. This biocatalytic cascade approach is enabling scalable methods for understanding PKS function, engineering biosynthetic enzymes and obtaining new bioactive molecules for analysis against drug-resistant pathogens.

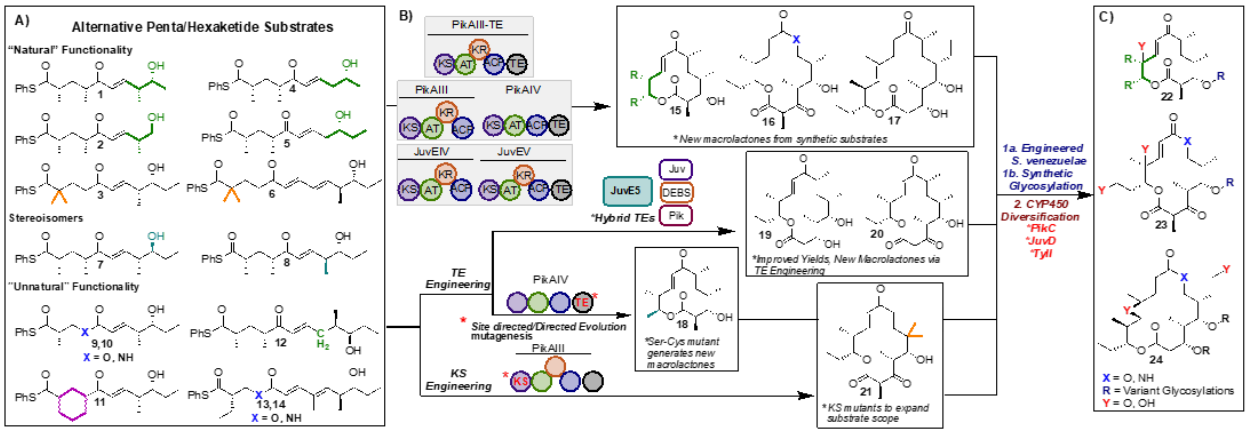

Figure 1. Strategies for engineering PKS systems for macrolactone diversification.

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ABOUT THE SPEAKERS

Sarah O'Connor received her degrees in chemistry from the University of Chicago (BSc) and MIT (PhD), and performed her post-doctoral work at Harvard Medical School. She was a Professor and Project Leader in Biological Chemistry at the John Innes Centre from 2011 to 2019. She has been the Director of the Department of Natural Product Biosynthesis at the Max Planck Institute of Chemical Ecology since summer 2019. Her research interests focus on plants' natural products, with a particular interest in the iridoids and alkaloids. Her research group takes a broad approach to understand plant biosynthetic pathways, ranging from gene discovery, mechanistic enzymology, and metabolic engineering. She has received the ACS Ernest Guenther Award in Natural Products (2022), Royal Society of Chemistry Perkin Prize for Organic Chemistry (2019); European Research Council (ERC) Advanced Grant (2018); Election to European Molecular Biology Organization (2017), Wain Medal (2013).

Xiaoguang Lei obtained BS in chemistry from Peking University in 2001 and Ph.D. in organic synthesis from Boston University under the supervision of Prof. John Porco in 2006. Then he conducted postdoc work with Prof. Samuel Danishefsky at Columbia University from 2006 to 2008. In early 2009, he returned to China and started his independent career as a Principal Investigator and Director of the Chemistry Center at the National Institute of Biological Sciences (NIBS) in Beijing. In early 2014, he received a tenured professorship from Peking University and moved to the College of Chemistry at Peking University. Now he is a Full Professor of Chemistry and Chemical Biology and a senior PI of the Peking-Tsinghua Center for Life Sciences. His primary research areas are chemical biology, natural product synthesis, synthetic biology, and drug discovery. He has published more than 140 original research papers, including Cell, Nature, Science, etc., and obtained 20 granted patents for new drug discovery. He has received many prestigious awards, including The 2022 MDPI Tu Youyou Award, The 2021 Boehringer-Ingelheim Investigator Award, The 2020 Bayer Investigator Award, The 2018 David Ginsburg Award in Israel, The 2017 Tetrahedron Young Investigator Award, The 2017 Swiss Chemical Society Distinguished Lectureship Award, The 2015 Chemical Society of Japan Distinguished Lectureship Award, The 2014 Roche Young Investigator Award, The 2013 International Chemical Biology Society (ICBS) Young Chemical Biologist Award, The 2013 Servier Young Investigator Award in Medicinal Chemistry, and The 2010 IUPAC Young Chemist Award, etc. Since 2017 he has served as an editor for Bioorganic & Medicinal Chemistry.

Jürgen Rohr's research focuses on natural product drugs, i.e. antibiotics, anticancer drugs and drugs against bone diseases. It includes the elucidation of complex multi-step biosynthetic pathways, carried out by bacteria, fungi or plants, with particular emphasis on enzyme mechanisms and generation of new natural products analogues through enzymatic syntheses. The results of these biosynthetic studies are used to generate modified natural product drugs through genetic pathway engineering. Before joining University of Kentucky, Dr. Rohr was Assistant and Associate Professor at The Department of Chemistry and Biochemistry of the University of Göttingen, Germany and Associate Professor at the Department of Pharmaceutical Sciences of the Medical University of South Carolina, Charleston, SC. He currently serves as Vice-Chair of UKCOP's Pharmaceutical Sciences Department.

ABOUT THE SPEAKERS

David H. Sherman is Hans W. Vahlteich Professor of Medicinal Chemistry at the University of Michigan Life Sciences Institute. Prof. Sherman received his B.A. in chemistry at UC Santa Cruz (1978) and Ph.D. in synthetic organic chemistry at Columbia University with Gilbert Stork (1981). After working at Biogen Research Corporation, he moved to the John Innes Institute as a research scientist with Sir Prof. David A. Hopwood (1987-1990). Following 13 years at the University of Minnesota, Prof. Sherman moved to the University of Michigan and is now the Hans W. Vahlteich Professor of Medicinal Chemistry, Professor of Chemistry, and Professor of Microbiology & Immunology. Sherman's laboratory is in the U-M Life Sciences Institute where his research focuses on the discovery and analysis of bioactive natural products and their metabolic pathways from diverse bacteria and fungi. Dr. Sherman was founding Director of the Center for Chemical Genomics at the University of Michigan Life Science Institute (2004 – 2013). He is current principal investigator of the UM Natural Products Biosciences Initiative.

Notable Awards: A. C. Cope Scholar Award (ACS), Fellow, American Association for the Advancement of Sciences (AAAS), Charles Thom Award (Society for Industrial Microbiology and Biotechnology), Distinguished Lecturer Award (American Society for Microbiology)

For more information please see: http://www.lsi.umich.edu/labs/david-sherman-lab

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ESAB aims to promote the development of Applied Biocatalysis and takes initiatives in areas of growing scientific & industrial interest in the field.

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27th January 2023 10.00-12.00 CET	Advances in the Analysis of Enzymatic Reactions organized by Roland Wohlgemuth and Jennifer Littlechild
24th February 2023 14.00-16.00 CET	Biocatalysis and Molecular Medicine organized by Jennifer Littlechild, Antonio Ballesteros, Thomas Sauter & Roland Wohlgemuth
24th March 2023 10.00 -12.00 CET	Synthetic Biology and Metabolic Engineering Tools and Methodologies organized by Frangiskos Kolisis and Roland Wohlgemuth

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