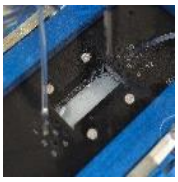
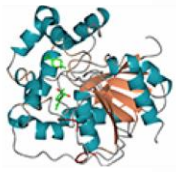
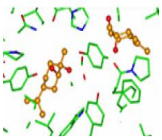
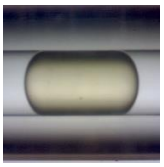





# ESAB Webinar

## *Biocatalytic Total Synthesis*

***May 27th 2022*** ***09.00-11.00 British Summer Time (BST)***
***10.00-12.00 Central European Time (CET)***
***16.00-18.00 China Standard Time (CST)***
***17.00-19.00 Japan Standard Time (JST)***
Chairs: Jennifer Littlechild (University of Exeter)
Roland Wohlgemuth (Lodz University of Technology)

## PROGRAMME

**10.00 CET Prof. Dr. Haruyuki Atomi, Department of Synthetic Chemistry and Biological Chemistry Graduate School of Engineering, Kyoto University, Katsura, Nishikyo-ku, Kyoto, Japan**

### What the archaeal genomes tell us

Archaea represent microorganisms that are phylogenetically distinct to members of Bacteria and Eukarya. Archaea and bacteria are both prokaryotes, but they display stark differences in the structure of their membrane lipids and machinery involved in DNA replication and transcription. In terms of metabolism, Archaea utilize enzymes and pathways that differ to their counterparts in bacteria and eukaryotes. Based on the archaeal genome sequences, there are numerous cases in which a particular metabolic pathway seems to be absent or incomplete. Our strategy is to search for the enzymes or pathways that replace the "missing" enzymes or pathways predicted from genome sequence data. We are studying the metabolism of the hyperthermophilic archaeon *Thermococcus kodakarensis*. Based on our strategy, we have identified structurally novel enzymes that cannot be identified by homology searches, as well as enzymes with novel activity. In this presentation, I will provide an overview of our metabolic studies on *T. kodakarensis*, focusing on the routes for biosynthesis.

**10.30 CET Dr. Benke Hong, Department of Natural Product Biosynthesis, Max Planck Institute for Chemical Ecology, 07745 Jena, Germany**

### Biosynthesis of Strychnine

Strychnine, a complex monoterpene indole alkaloid, was isolated from the seeds of *Strychnos nux-vomica* (poison nuts), which have been used in traditional medicine in China and South Asia. Strychnine played a significant role in the field of chemistry for centuries during its isolation, structure elucidation and synthesis. The fascinating polycyclic architecture inspired chemists to develop new synthetic transformations and strategies. However, it is still unknown how plants create this complex structure. Here we report the biosynthetic pathway of strychnine, along with the heterologous production of this molecule in *Nicotiana benthamiana.*

**11.00 CET** **Prof. Dr. Yong Wang, Key Laboratory of Synthetic Biology, CAS, CAS Center for Excellence in Molecular Plant Science (CEMPS), Institute of Plant Physiology and Ecology, Chinese Academy of Sciences (CAS), Shanghai 200032, China**

**Bamboo and Crop Leaves Biosynthesize Antinociceptive C-glycosylated Flavones**

C-glycosylated flavones (CGFs) are promising candidates as anti-nociceptive compounds. The leaves of bamboo and related crops in the grass family are a largely unexploited bioresource with a wide array of CGFs. We report here pathway-specific enzymes including C- glycosyltransferases (CGTs) and P450 hydroxylases from cereal crops and bamboo species accumulating abundant CGFs. Mining of CGTs and engineering of P450s that decorate the flavonoid skeleton allowed the production of desired CGFs (with yield of 20–40 mg/L) in an Escherichia coli cell factory. We further explored the antinociceptive activity of major CGFs in mice models and identified isoorientin as the most potent, with both neuroanalgesic and anti-inflammatory effects superior to clinical drugs such as rotundine and aspirin. Our discovery of the pain-alleviating flavonoids elicited from bamboo and crop leaves establishes this previously underutilized source, and sheds light on the pathway and pharmacological mechanisms of the compounds.

**11.30 CET** **Prof. Dr. Jason Micklefield, Department of Chemistry and Manchester Institute of Biotechnology, The University of Manchester, Manchester M1 7DN, UK**

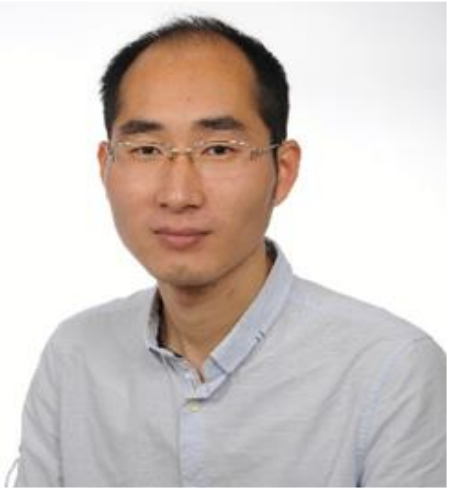
**Discovery, characterisation and engineering synthetic pathways to bioactive molecules**

Jason Micklefield is a Professor of Chemical Biology with extensive experience in natural product biosynthesis, pathway engineering and biocatalysis.[1-6] His lab developed new methods for engineering complex NRPS enzymes that deliver antibiotics including enduracidin and CDA.[2,7] They have discovered and characterised new pathways possessing hybrid NRPS-PKS assembly lines producing the structurally unique antibiotic K16[3] and TMC-86A from the epoxyketone family of proteasome inhibitors now widely used antitumour agents.[8] JM's team also discovered and determined structures of novel ATP-dependent ligase enzymes, from PKS-NRPS pathways to phytotoxins, which were engineered to produce agrochemicals and pharmaceuticals including drugs in clinical trials for COVID-19.[1] New synthetic biology approaches were also used to create a *de novo* pathway to "non-natural" thaxtomin phytotoxin derivatives, with improved stability, that are of industrial interest as herbicides for crop protection.[9] In addition to biosynthesis, JM is widely recognised for his research in biocatalysis. His lab employed structure-guided mutagenesis and directed evolution to improve activity, expand the substrate scope and switch the regioselectivities of halogenase enzymes.[10,11] They showed how engineered halogenases can be integrated with Pd-catalysed cross-coupling chemistry, in one-pot reactions, to affect the direct regioselective arylation, alkenylation, cyanation and further functionalisation of C-H positions in various aromatic scaffolds.[4,6] JM's lab also characterised various methyltransferases (MT), demonstrating how these can be used in the regioselective alkyl-diversification of tetrahydroisoquinolines, rapamycin immunosuppressive agents and other bioactive natural and non-natural products.[12-16] His lab succeeded in engineering orthogonal MT creating alternative bioalkylation pathways[13] and developed methods for selective derivatisation of tyrosine residues in peptides and proteins using MT and SAM analogues for labelling and other applications.[16] The team characterised, engineered and developed aryl malonate decarboxylases,[17] aminomutases/lyases,[18] tryptophan synthase[19] and other important biocatalysts. Previously, JM's group also succeeded in re-engineering the first orthogonal riboswitches (genetic tools & biosensors) in diverse bacterial species including *Bacillus*.[20-22]

References: [1] Winn *et al* *Nature* **2021**, *593*, 391; [2] Thong *et al* *Nature Commun* **2021**, *12*, 6872; [3] Law *et al* *Nature Catalysis* **2018**, *1*, 977; [4] Craven *et al* *Nature Catalysis* 2021, *4*, 385; [5] *Bering et al* *Nature Commun* **2022** *in press*; [6] Latham *et al* *Nature Commun* **2016**, *7*, 11873; [7] Thirlway *et al* *ACIE* **2010**, *51*, 7181; [8] Zabala *et al* *JACS* **2016**, *138*, 4342; [9] Winn *et al* *ACIE* **2018**, *57*, 6830; [10] Menon *et al* *ACIE* **2017**, *56*, 11841; [11] Shepherd *et al* *Chem Sci* **2015** *6*, 3454; [12] Bennett *et al* *ACIE* **2018**, *57*, 10600; [13] Herbert *et al* *ACIE* **2020**, *59*, 14950; [14] Law *et al* *Chem Sci* **2015**, *6*, 2885; [15] Law *et al* *ACIE* **2016**, *55*, 2683; [16] Struck *et al* *JACS* **2016**, *138*, 3038; [17] Okrasa *et al* *ACIE* **2009**, *48*, 7691; [18] Chesters *et al* *ACIE* **2012**, *51*, 4344; [19] Francis *et al* *ChemBioChem* **2017**, *18*, 382; [20] Dixon *et al* *PNAS* **2010**, *107*, 2830; [21] Wu *et al* *JACS* **2015**, *137*, 9015; [22] Robinson *et al* *JACS* **2014**, *136*, 10615.

## ABOUT THE SPEAKERS

**Professor Dr. Haruyuki Atomi** studied at the Department of Industrial Chemistry, Graduate School of Engineering, Kyoto University and received his PhD in 1992. He then became an Assistant Professor at the same Department until 1997, studying yeast metabolism and physiology. He also carried out postdoctoral research at the University of Stuttgart, studying protein engineering of lipases. From 1997, he became Associate Professor at the Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University, and switched topics, starting research on thermophiles and archaea. In 2009, he became Professor at this department and continues his work on the physiology of archaea. He has chaired a number of international meetings and is now President of the International Society for Extremophiles.



**Dr. Benke Hong** is a postdoctoral researcher in the Department of Natural Product Biosynthesis at the Max Planck Institute for Chemical Ecology since 2019. He received his B.Sc. degree in pharmaceutical engineering from Liaoning University (P. R. of China) in 2011. He then joined Professor Xiaoguang Lei's group at National Institute of Biological Sciences (NIBS) in Beijing to start his Ph.D. studies on the total synthesis of bioactive natural products. After receiving his Ph.D. degree in 2016, he stayed in the same group at Peking university as a research assistant in chemical biology. In 2019, he moved to Germany to conduct his postdoc with Prof. Sarah O'Connor.

**Prof. Dr. Yong Wang** is Professor/Principal investigator/Deputy director of the CAS-Key Laboratory of Synthetic Biology, CAS Center for Excellence in Molecular Plant Sciences, Chinese Academy of Sciences (CAS). He obtained his Ph.D. degree of biochemical engineering from East China University of Science & Technology, China in 2004 and was trained as a postdoctoral fellow at Department of Chemical and Biological Engineering in Tufts University, USA during Feb 2005 to Aug 2008. His research is centered on the design and assembly of recombinant microorganisms for the production of complex natural products. A particular focus is the elucidation of design principles for the production of unnatural natural compounds within the framework of the nascent field of synthetic biology.
Major Research Areas: Synthetic Biology; Metabolic Engineering; Biochemical Engineering; Bioprocess Engineering. More than 90 papers have been published.

## ABOUT THE SPEAKERS

**Prof. Dr. Jason Micklefield** is Professor of Chemical Biology within the School of Chemistry and the Manchester Institute of Biotechnology. He graduated from the University of Cambridge in 1993 with a PhD in Chemistry, working with Prof Sir Alan R. Battersby FRS to complete the first total synthesis of haem d1. He then moved to the University of Washington, USA, as a NATO postdoctoral fellow investigating various biosynthetic pathways and enzyme mechanisms with Professor Heinz G. Floss. In 1995 he began his independent research career as a Lecturer in Organic Chemistry at Birkbeck College, University of London before moving to Manchester in 1998. The Micklefield Lab develop more sustainable bio-inspired ways to build molecules. Our lab has an eclectic philosophy and is highly interdisciplinary, engaged in Chemical and Synthetic Biology research tackling diverse challenges at the Chemistry-Biology interface. We exploit techniques and knowledge from organic chemistry and enzymology through to molecular microbiology and genetics to develop sustainable routes to target molecules for therapeutic and other applications. The main research themes include: 1) Biosynthesis and biosynthetic pathway engineering providing novel bioactive natural products particularly new antibiotics to combat antimicrobial resistance (AMR) and treat neglected diseases; 2) Biocatalysis & integrated catalysis – Enzyme discovery, characterisation & engineering for enzymatic synthesis. Merging chemo- and biocatalysis for telescoping more sustainable routes to pharmaceuticals and other valuable products; 3) Nucleic acids chemistry and biology, including developing new routes to nucleic acid therapeutics (NAT) and functional tools such as riboswitches and aptamers.

## NEXT ESAB WEBINARS

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

Schedule and Topics of the next ESAB webinar:

| | |
|---|---|
| 24th June 2022<br>14.00-16.00 CET | Biocatalysis and Sustainable Chemistry, joint ESAB-SusChem Webinar, organized by Andrés R. Alcántara and Pablo Domínguez de María, ESAB Working Group Sustainable Chemistry |
| 29th July 2022<br>10.00-12.00 CET | Biocatalysis and Molecular Medicine, organized by Roland Wohlgemuth, Jennifer Littlechild and Thomas Sauter |

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Personal membership is free.

Institutional membership is welcome and is currently being established as new membership category.

ESAB has been founded in 1980 and has the mission of promoting the development of Applied Biocatalysis throughout Europe. The aims of ESAB are to promote initiatives in areas of growing scientific and industrial interest of importance within the field of Applied Biocatalysis.

Further information can be found on the ESAB website www.esabweb.org

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