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In the Lab

Artificial Metalloenzymes for Sustainable Chemical Production

***Johnson Matthey Technology Review* features laboratory research**

NON-PEER REVIEWED FEATURE

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Amanda G. Jarvis is a Senior Lecturer and Future Leaders Fellow in the School of Chemistry at the University of Edinburgh, UK. She started her career in the field of ligand design and coordination chemistry, before moving to working on homogeneous catalysis with carbene and nitrene intermediates. She subsequently developed an interest in combining these areas with biology, moving into the field of artificial metalloenzymes in the group of the late Professor Paul Kamer at the University of St Andrews, UK, where she was awarded a Marie Curie Individual Fellowship to work on artificial metalloenzymes for selective oxidation. She moved to Edinburgh to start her independent career with a Christina Miller Fellowship in 2017, before receiving a prestigious UK Research and Innovation (UKRI) Future Leaders fellowship in 2019 allowing her to build up her research group. The group's focus is to bring transition metal chemistry into the biocatalytic toolbox, allowing new reactions to take place *in vivo* or in cascade reactions with natural enzymes. She serves on the Royal Society of Chemistry (RSC) Applied Catalysis Interest group committee and chairs the UK Catalysis Hub's Early Career Researcher committee.

About the Researcher

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About the Research

Enzymes are often regarded as the ideal catalysts: able to perform difficult reactions, for example converting methane to methanol, under mild conditions and with excellent rates and stereoselectivities. For decades chemists have

used enzymes as inspiration for catalyst design, and more recently enzyme engineers have shown it is possible to engineer enzymes to perform new-to-nature reactions providing exciting new vistas in catalysis (1). The latter relies on small amounts of promiscuous activity in an existing enzyme and is therefore limited to reactions similar to the native reaction mechanism. In contrast many industrial catalytic processes rely on metal-based mechanisms that are not known in nature such as carbonylation and oxidative addition/reductive elimination. The Jarvis group aims to bring these reaction classes into the biocatalytic toolbox by combining synthetic transition metal catalysts with protein scaffolds for selective chemical synthesis. The group predominantly explores late-transition metal-catalysed reactions such as C–H functionalisation, cross-coupling reactions, carbonylation and hydroformylation. The latter is the most advanced project and is currently sponsored by Johnson Matthey.

The molecular binding properties of protein scaffolds can be used to control substrate binding orientation towards the metal centre and thus reaction selectivity. The steroid carrier protein from the human multifunctional enzyme 2 (SCP-2L) contains a hydrophobic tunnel, in which different metal complexes can be placed. This approach was used to successfully design a rhodium-based metalloenzyme for biphasic hydroformylation of long chain alkenes. The Kamer group developed a two-step approach for incorporating phosphine ligands into protein scaffolds containing a unique cysteine residue, and this approach was utilised to add a triphenylphosphine derivative into SCP-2L (2). Complexation with Rh(acac)$(CO)_2$ gave rise to a rhodium metalloprotein, which was characterised by ^{31}P nuclear magnetic resonance, mass spectrometry and extended X-ray absorption fine structure (EXAFS) (3). The resulting hydroformylase was able to catalyse the biphasic hydroformylation of C8 to C18 alkenes, with turnover numbers (TON) of up to 400 observed for 1-octene (**Figure 1**) (4). Remarkably, good linear selectivity was observed of up to 80% linear aldehyde, even though only one phosphine ligand was present per enzyme. Work is ongoing to explain the origin of the activity, with EXAFS data potentially highlighting a rhodium-sulfur interaction from a nearby methionine. This would provide a bidentate-type coordination mode known to increase linearity, albeit with sulfur coordination which is commonly considered a catalyst poison.

Artificial metalloenzymes are engineerable using traditional bioengineering approaches to enhance their stability or to tailor their reaction specificity. For example, using computational approaches, including a 3DM database from Bio-Prodict BV, The Netherlands, which aligns protein superfamilies *via* structural similarity, a series of mutations were suggested to increase the thermostability of the hydroformylases (5). A mixture of mutations including consensus mutations, those to introduce salt-bridges and mutations to stabilise the structural folds were tested, with the latter two showing the best increases in the melting temperature (T_m) of the hydroformylases. In turn, this allowed the hydroformylases to be utilised at a higher temperature, improving reaction rate.

Current work on the hydroformylases is looking to expand the substrate scope, with a focus on substrates that can be made microbially from biomass, such as styrene and unsaturated fatty acids. This will allow hydroformylation to move from a classic petrochemical based industrial reaction into the world of biocatalysis. A long-term aim is to be able to conduct *in vivo* hydroformylation to

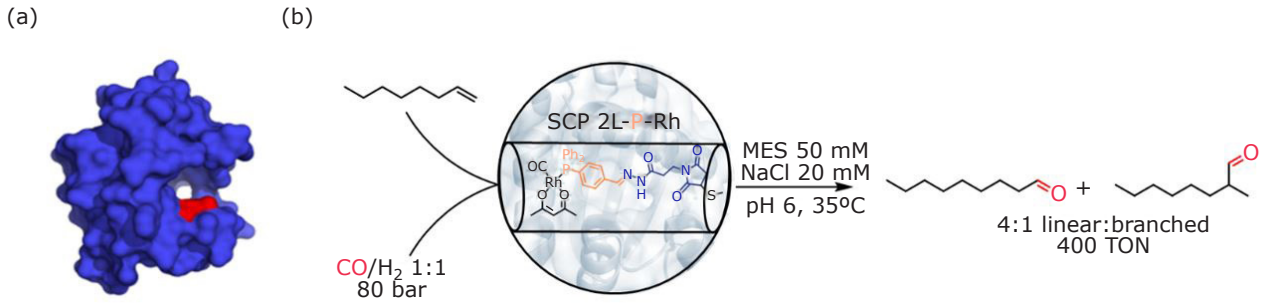

Fig. 1. (a) Space-filled model of SCP-2L (PDB: 1IKT); (b) scheme depicting the hydroformylation of 1-octene using rhodium hydroformylases

lead to fermentation as a viable large-scale route to aldehydes.

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