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Building and optimizing multi-enzyme *in vitro* cascade reactions

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Biocatalysis is becoming increasingly attractive for the development of more efficient and cleaner chemical synthetic processes. The combination of multiple enzyme steps for cascade reactions allows for attractive one-pot processes with reduced operating costs. While the use of whole-cells have a number of advantages for these reactions, the competing needs of the cell and limited transport across the cell membrane can result in a low final product concentration. In contrast, the use of isolated enzymes allows reactions to be easily controlled, with the use of stable enzymes such as those from thermophiles offering economically competitive processes. For the construction of novel enzymatic cascade reactions, there is a need for well-defined modular enzyme building blocks that can be quickly assembled for new reactions. Carboxylic acid reductase (CARs) is a relatively undeveloped class of enzyme which meets a demand in synthetic chemistry for a green and regiospecific route to aldehydes from their respective carboxylic acids. A thorough biochemical characterization of four new CARs provides insight into the operating parameters of these enzymes, while the integration of a CAR into a seven enzyme *in vitro* cascade reaction demonstrates their potential for green chemistry. Mathematical modeling of the cascade allows for a detailed understanding of the reaction and gives opportunity for its optimization with respect to flux and cost. Our work highlights the virtue of thorough enzyme characterization, and of modeling reactions, to deliver new understanding and build robust pathways.

Biography

Nicholas Harmer completed his PhD in the laboratory of Professor Sir Tom Blundell in Cambridge, UK, researching the structure and interaction of fibroblast growth factors, their receptors, and heparin. Following this, he took a Post-doctoral position in Cambridge, investigating the structure and function of a range of signaling proteins and bacterial enzymes. He then moved to AstraZeneca R&D Mölndal, Sweden, where he worked as a Structural Biologist in Drug Discovery. In 2007, he established his own laboratory at University of Exeter, UK. His research work focusses on Synthetic Biology and Drug Discovery applications for neglected diseases. His main interest is in understanding enzymes more deeply, and in exploiting this understanding to develop useful chemicals and biochemical. In 2017, he moved to Living Systems Institute, Exeter.

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