TOWARDS HIGH-VALUE CHEMICALS PRODUCTION HARNESSING SYNTHETIC BIOLOGY

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We aim to design and construct organisms with new functionalities of unprecedented scope, by exploiting synthetic biology for metabolic engineering; e.g. by harnessing our ability to readily sequence complete genomes and to rewrite/re-design pathways on a large scale.

We explore these possibilities in the context of high-value chemical production, utilising the Design/Build/Test/Learn cycle at the Parts, Devices and Systems level. Many microorganisms already have the machinery to produce diverse bioactive molecules that can be used in health, agriculture and food (Cimermancic et al., *Cell* 2014). As a first step towards re-engineering these high-value chemical biosynthesis pathways for enhanced productivity and diversity, we aim to understand the interchangeability of biosynthetic parts (Diez et al., *ACS Synth Biol* 2015) and created a minimal information database for natural products with the support from the natural products community (Medema et al., *Nature Chem. Biol*. 2015). We have designed and assembled pathways using the identified parts (Leferink et al., *ChemistrySELECT* 2016) and will engineer orthogonal transcription mechanisms (based on signalling molecule circuits (Biarnes-Carrera et al., *Curr. Opin. Chem. Biol.* 2015) and bacterial microcompartments (Chessher et al., *ACS Biomater. Sci. Eng.* 2015). In addition, we are expanding our collection of computational tools for the detection and analysis of secondary metabolite biosynthesis gene clusters, to enrich our library of parts and building blocks for pathway engineering (Weber et al., *Nucl. Acids Res.* 2015). We also use computational modelling (constraint-based descriptions of bacterial metabolism) to identify suitable overproduction hosts and pinpoint biosynthetic bottlenecks to target for further cellular engineering in a synthetic biology strategy (Breitling et al., *ACS Synth. Biol.* 2013). And finally, we combine this analysis with high-resolution mass spectrometry analysis, which we also employ for the debugging of the engineered systems (Jankevics et al., *Metabolomics* 2012).

We have these tools in the Design/Build/Test/Learn cycle of the recently established BBSRC/EPSRC-funded Manchester Synthetic Biology Research Centre, SYNBIOCHEM, where they provide a platform for the high-throughput engineering of fine and speciality chemicals production in microbial systems.