The bipartisan future of synthetic chemistry and synthetic biology

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Small molecule synthesis from oil and natural gas forms the foundation of multiple billion-dollar industries. Yet this is inherently unsustainable due to the non-renewable nature of fossil fuels. Chemical synthesis is also a major driver of climate change, with bulk chemical production emitting >36 million tonnes of CO_2 in Europe alone in 2019[1]. The pharmaceutical industry is also major contributor, emitting >48 Mt of CO_2 per million dollars annual turnover, 55% more than that of the automotive industry[2]. Additionally, millions of tonnes of fossil fuels have been channelled into the production of single use plastics, causing further environmental damage. The evidence is clear that continuing our current trajectory is both physically unsustainable and irreversibly damaging to our planet, carrying a threat to human health both now and to future generations.

The scientific community have responded with a suite of novel technologies for sustainable chemical synthesis. Synthetic biology in particular has gained significant traction, not least due to its ability to utilise waste and renewable feedstocks for the production of chemicals and pharmaceuticals[3–6]. Yet synthetic biology is inherently limited by the reactions known to Nature, precluding its ability to access vast swathes of chemical space. Forecasts estimate that only ~20% of the chemical industry can be replaced by a bio-based alternative, with processes such as metathesis and cross-coupling currently reliant on chemical approaches.

A sustainable future in this field requires a more holistic approach. Combining the versatility and scope of chemical catalysis with the ability of synthetic biology to valorise waste-derived or renewable building blocks holds a wealth of opportunity to access areas of chemical space, which would not be accessible using synthetic biology alone (Figure 1). This approach leverages 140 years of innovation in organic chemistry in a new context, eliminating the need to engineer a new enzyme to replace every chemical reaction[7].

This young field has already demonstrated potential. For example, interfacing an *E. coli* styrene production pathway with iron catalysis enabled preparation of cyclopropanes in a sustainable, one-pot synthesis from glucose and would not be possible using chemical or biological methods alone[8]. Microbes have also been shown to exhibit inherent reactivity on small molecules[9,10], which may be combined with chemical catalysis to access novel targets. Further examples demonstrate chemical hydrogenation being replaced with bio-based H_2 gas[11], whilst Fenton chemistry driven by mediator molecules produced by a brown rot fungus has been used to expedite the degradation of lignin[12]. Artificial metalloenzymes also represent a promising avenue in this field, enabling new-to-nature chemistry such as metathesis[13] and Pd catalysed C-C cross coupling[14] to occur within living cells. The recent surge in interest in waste lignin and plastic degradation and valorisation has also highlighted a wealth of untapped possibilities for the circular economy, to date demonstrated using synthetic biology[15,16] or synthetic chemistry[17] in isolation.

Whilst the examples discussed above take advantage of chemical reactivity in biological systems, there are also traits specific to synthetic biology which will aid the development of novel hybrid processes for chemical synthesis. Firstly, microorganisms have an inherent ability to respond to environmental stimuli, which may be harnessed to direct metabolic flux toward target chemical production. For example, TetR family derived genetically encoded sensors have been rationally designed to control gene expression in response to molecular signals[18]. In a second example, chimeric LuxR transcription factors have been engineered to activate the expression of biosynthetic gene clusters[19]. Synthetic biology can also be employed to confer decision-making behaviours on biological systems, such that metabolic functions can be controlled in response to external stimuli. Examples of this include engineering allosteric transcriptional repressors to enable biological activity to be turned off or on in response to chemical signals[20] and control of pathway enzyme levels using a protein degradation tag, enabling the decoupling of bacterial growth and chemical production phases[21]. In the context of interfacing chemical and biological catalysis, strategies such as these will enable microorganisms to be treated as continuous feedback devices for process optimisation, in addition to their role in the engineered pathway. Finally, the young field of microbial consortia engineering offers a promising strategy for compartmentalisation of non-compatible steps in a pathway[22,23]. Whilst most examples to date focus on the

production of target chemicals using synthetic biology alone[24,25], merging microbial consortia with chemical catalysis could enable otherwise inaccessible pathways and the production of molecules of ever increasing complexity.

Whilst significant progress has been made in the field, the potential of blending these two disciplines remains largely untapped. Yet with the ever decreasing cost of DNA synthesis, increasingly rapid design and optimisation of biological systems, and a vast array of chemical catalysts now available, the field of chemical synthesis has an unprecedented opportunity to move towards a sustainable future, embracing the best of synthetic biology and synthetic chemistry.

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Captions to figures:

Figure 1. Interfacing chemical catalysis with synthetic biology enables access to a vast area of chemical space not accessible using synthetic biology alone.

Figure 2. Chemical catalysis can be integrated with engineered microbes for production of value-added small molecules using renewable feedstocks or waste materials as a substrate.

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Synthetic biology holds great potential for sustainable chemical synthesis, yet is limited to accessing a relatively small area of chemical space. By interfacing this new technology with the versatility and scope of synthetic chemistry, the best of both worlds can be harnessed to drive a green chemical industry.