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SYNBIOCHEM Synthetic Biology Research Centre, Manchester – A UK foundry for fine and speciality chemicals production

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ABSTRACT

The UK Synthetic Biology Research Centre, SYNBIOCHEM, hosted by the Manchester Institute of Biotechnology at the University of Manchester is delivering innovative technology platforms to facilitate the predictable engineering of microbial bio-factories for fine and speciality chemicals production. We provide an overview of our foundry activities that are being applied to grand challenge projects to deliver innovation in bio-based chemicals production for industrial biotechnology.

In 2012, the UK Synthetic Biology (SynBio) Roadmap Coordination Group published the first UK SynBio roadmap [1] that set out a clear strategic vision recognising the enormous contribution that SynBio, as a key set of underpinning technologies, could make to industrial biotechnology and thus the UK bio-economy. The recommendations included sponsoring a network of multidisciplinary research centres, building a skilled, energised and well-funded UK SynBio community, investing to responsibly accelerate technology to market and establishing a SynBio leadership council. The updated Synthetic Biology Strategic Plan of 2016 [2] builds on these recommendations to accelerate the commercial translation of SynBio advances, support industrialisation and commercialisation, safeguard the capacity of the innovation pipeline, expand the expert workforce and further develop national and international partnerships. The total public sector investment in UK SynBio over the last 8 years has totalled > £300 M and is amongst the largest per capita in the world. Through this timely investment the UK has established a comprehensive national network comprising Synthetic Biology Research Centres (SBRCs), DNA synthesis facilities, Centres of Doctoral Training and a national Innovation and Knowledge Centre to help drive commercial innovation.

Manchester was the global industrial hub at the heart of the 19th-century industrial revolution, when technological advances transformed the industrial landscape and impacted across all aspects of everyday living [3]. At the beginning of a new 21st-century bio-industrial revolution, it is fitting that once again Manchester is taking a leading role. Building on a proud tradition in pioneering the use of biological fermentation processes for chemical production (initiated by Chaim Weizmann in Manchester [4]) and as the historical home of chemical engineering [5], SynBio research in Manchester is focusing on innovative developments to accelerate the biological production of diverse high-value chemicals. Through

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the establishment of Manchester's national SBRC, SYNBIOCHEM (www.synbiochem.co.uk), we have united our expertise from across the foundational sciences, including biological catalysis, metabolic engineering, systems biology and computational modelling to deliver a foundry for metabolic engineering focused on delivering new SynBio tools/technologies for the production of fine and speciality chemicals for industrial biotechnology.

Bio-based chemical production processes are already delivering major economic impact for industrial biotechnology [6], but there is huge potential for SynBio tools and techniques to dramatically enrich and expand bio-based production routes to address societal grand challenges relating to sustainable energy, climate change, environmental protection and health, providing processes with reduced toxic by-products, lower fuel consumption, reduced carbon footprint and enhanced stability of supply. Early SynBio breakthroughs have generally focused on the delivery, fine-tuning and optimised microbial production of individual chemical products, such as the antimalarial precursor artemisinic acid [7] or various opioids in yeast [8–10 for reviews]. The next generation of SynBio innovations in Manchester is now directed towards the engineering of chemical novelty and diversity, targeting metabolic processes in microorganisms to produce an impressive range of important chemicals, and high concentrations of industrially important compounds from antibiotics [11] and vitamins to industrial flavours, fragrances and pigments [12]. Recent examples from SYNBIOCHEM programmes, built on the well-established fundamental research in the Manchester Institute of Biotechnology (MIB, www.mib.ac.uk), that have already delivered new intellectual property, include the development of tools and microbial factories/hosts relevant to the production of pravastatin [13], biosynthetic menthol [14] and propane [15]; the development of new regulatory components (e.g., riboswitches [16]); and the discovery of new biocatalysts for chemicals production that provide new routes to alkenes [17,18] and enantiopure amines [19]. These are supported by unique technology innovations in DNA design and assembly [20,21] that underpin the rapid construction and evolution of new parts and pathways through, for example, new approaches to directed evolution [22,23]. Many of these discoveries are subject to new SYNBIOCHEM patent submissions, and the work on bio-propane has supported the formation of an early spinout company, C3BioTechnologies Ltd.

The University of Manchester's SYNBIOCHEM Centre builds on a wealth of expertise at the MIB and across campus to provide rapid, predictable delivery of new microbial platforms for the production of fine chemicals through a versatile suite of integrated technology platforms that move us towards a "*dial-a-molecule*" capability, which can be focused on a wide range of chemical targets. Co-directed by Professors Nigel Scrutton, Eriko Takano and Nicholas Turner, the Centre unites 29 research groups supported by an expert team of Senior Experimental Officers to implement the Centre's challenge-led collaborative science programmes. A rapidly expanding SynBio toolbox is enabling our metabolic engineers to exploit the inherent biosynthetic capacity of microorganisms and to divert metabolic resources to the production of diverse renewable speciality chemicals. We are harnessing new capabilities in the rational design of new genetic circuits and pathways for the production of fine chemicals and the targeted discovery of new chemical entities with potential bioactive properties which may provide benefits across a wide range of applications [24].

A major focus for the Centre is the fully automated integration of our tools to create a cyclical Design–Build–Test production pipeline (Fig. 1) that is flexible, provides access to a wide range of chemical space, and allows us to deliver projects from the rational *in silico* design of parts, circuits and pathways, to their assembly and testing in engineered microbes, and through iterative cycles of learning and informed re-design. This unique capability of SYNBIOCHEM offers a comprehensive suite of platform technologies for focused grand challenge projects.

The Centre's **Design** platform is developing a suite of *in silico* tools to support the design of synthetic metabolic pathways [25]. These tools cover enzyme selection, design of reusable genetic parts (including ribosome binding site and codon optimisation), intelligent sampling of combinatorial design space through a Design of Experiments approach, and support of pathway assembly methods. This work builds on our strong foundation in the development of genome mining tools, such as antiSMASH [26], and automated pipelines for cheminformatics and biosynthetic pathway prediction, such as RetroPath and related tools [27–30]. The recent development of SensiPath, for the enhanced design of metabolic pathways with intermediates that are detectable by biosensors and therefore amenable to high-throughput screening, further expands this growing arsenal of design tools [31]. Underpinning much of these design approaches is expertise in systems biology and metabolic modelling [32–34], allowing *in silico* simulations to drive each iteration of the Design-Build-Test-Learn cycle. Throughout this work, the Centre is committed to the support of and further development of community standards including SBOL [35] and SBOL Visual [36].

Based on the resulting design blueprints, the **Build** platform is responsible for the manufacturing of catalytic, regulatory and structural parts; assembly of these parts into pathways, circuits and microbial scaffolds; and engineering of the chassis for efficient biosynthesis of target compounds with high product yields. We have automated our DNA assembly methods including the efficient construction of directed evolution libraries, that allow the rapid optimization of the enzyme building blocks of our synthetic pathways (SpeedyGenes [20]), and are currently developing more efficient selective library generation methods. Growth of our collection of structural, regulatory and bio-catalytic parts is benefiting from automated high-throughput (HTP) preparation and quality control. We are harnessing our new robotics platforms for automated combinatorial pathway assembly, chassis growth and target production (media dispensing, colony picking, and automated HTP growth, through to automated metabolite and compound extraction), to rapidly assemble and screen diverse part libraries and biochemical pathways, and to phenotypically characterize our engineered microbial systems. We are developing a regulatory and biosensor toolkit to facilitate real-time control, sensing and quantification of specific products, intermediates or cofactors from engineered pathways in living cells, enabling high-throughput screening and selection. Novel riboswitches are being constructed from target-specific aptamers (identified through our automated SELEX platform), building on our experience in developing orthogonal riboswitches as gene regulatory tools [37]. Pathway-specific biosensors are also being constructed using sensitive transcription factor/operator pairs identified through the mining of next-generation transcriptome sequencing data. Picodroplet (SphereFluidics) and fermentation platforms provide the Centre with capabilities for microbial production and analysis from single cell level through to multi-litre scale. Optimisation at the laboratory scale will inform further collaborative development and evaluation at larger pilot scales.

Our **Test** platform, built on a wealth of expertise in targeted analytics and untargeted metabolomics [38,39], is utilising an integrated suite of high-throughput screening methods for the quantification of optimised target compound production, assaying target metabolites and enzymes, as well as tracking pathway intermediates and undesired side products or potential metabolic bottlenecks. Our comprehensive state-of-the-art targeted and untargeted mass spectrometry platforms are being applied for

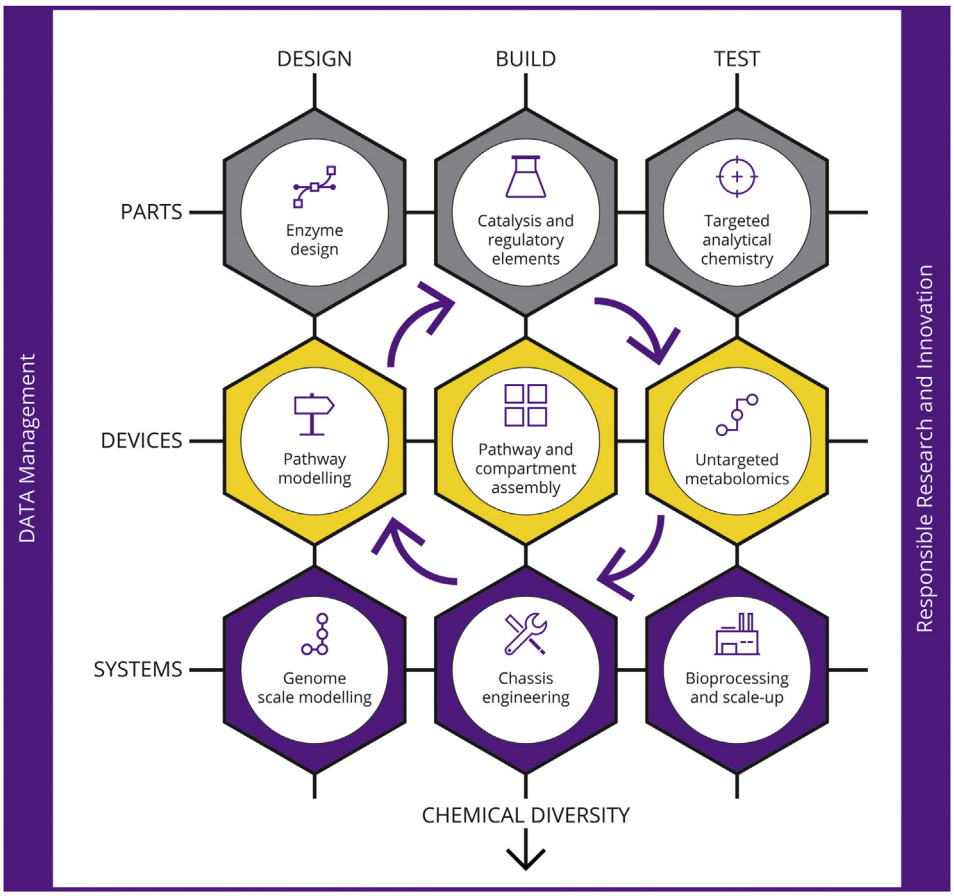

Fig. 1. The integrated SYNBIOCHEM pipeline to chemical diversity.

metabolomic profiling of molecular species of interest, and a dedicated ion mobility platform provides additional discriminative power for compound identification. We are signal processing and deconvolving our data using a range of open source tools, including our evolving mzMatch toolbox [40], to provide rapid information to inform the iterative re-design, debugging and optimisation of our production strains. Our dedicated integrated infrastructure provides seamless forward and backward data traceability across analysed experimental data and models. We are using an iterative active learning strategy for experimental planning to ensure the generation of high-quality training sets that are used at each iteration to refine and update the models. The Centre is applying machine-learning workflows trained on the analysed data to learn sequence- and structure-activity relationships [22,28] that feed back into the Design platform. Similarly, a growing catalogue of predictive tools that learn from resulting data is applied to the redesign of additional SynBio components, from chemical diversity discovery to strain and process optimization [25,41].

Our integrated Design–Build–Test platforms are being applied to a selection of "grand challenge" projects that target key chemical scaffolds including: Alkaloids, which constitute a vast range of plant-derived compounds with potent bioactivities and are a source of numerous drugs and drug precursors [42]; Flavonoids, traditionally of plant origin with many desirable properties and used as antibacterial, antitoxin, antiviral and antifungal agents [43]; and Terpenoids, a valuable class of molecules with a range of uses from flavours and fragrances to antimalarial drugs and biofuel precursors [44]. SynBio-derived chemical ingredients have already reached the food and cosmetics market, with companies now focusing on the production of purified fine chemicals (e.g. nootkatone fragrance) which once extracted are considered as "natural" and do not require labelling of the resulting product as containing genetically modified organisms. It is, however, early days and the development of consumer responses to more widespread use of SynBio ingredients remains to be seen [45]. Pre-market regulation of SynBio products and specifically the production processes that use synthetically modified organisms (SMO's) will need to be carefully considered to ensure continued public acceptance. The recent development of three official Opinion documents by the Scientific Committees of the European Commission on potential risks of SynBio and the associated research needs [46–48] is an important contribution to this process.

Moreover, complementing our core science programmes, SYNBIOCHEM's Responsible Research and Innovation (RRI) platform is developing major programmes on the societal aspects faced by SynBio, including real-time assessment and anticipation of research and innovation trajectories, deliberation and reflection on emerging ethical, regulatory and policy issues, and collaborative research development. SYNBIOCHEM's RRI platform seeks to initiate early multiway dialogue, provide expertise, guidance and training in the responsible governance of SynBio innovation, and foster public engagement and training for the research community, in order to anticipate, prepare for and if necessary mitigate the impacts of SynBio technology in the wider society, economy and environment [49]. Examples of the Centre's activity in this domain include contributions to European Commission reports on SynBio

safety issues [50], involvement in establishing a good practice framework – The www.Responsibility-Navigator.eu [51], and the publication of a comprehensive sociological analysis of SynBio as an emerging scientific field [52].

In summary, SYNBIOCHEM is addressing major SynBio challenges, employing its foundry concept and integrated technology platforms to facilitate the predictable engineering of microbial biofactories for chemical production. Through its open collaborative ethos the Centre is proactively engaging with academic and industrial partners, not only in the UK but also on the international stage. Development of industrial collaborations, foresight and awareness is a major focus of the Centre. We are accelerating the commercial translation of our activities through continued dialogue with industrial partners that is enabled through joint co-funded research projects, that target and apply our technologies to commercially relevant chemicals at an early stage (e.g. a collaboration with DSM on a single step fermentative production route for pravastatin [13]), industry funded PhD studentships and close partnerships with instrument developers. Building on our existing productive UK and EU collaborations, the Centre is working closely with the other UK SBRCs with joint projects, workshops and events, whilst international partnerships are providing broader access to technologies and expertise. Examples are UK research council co-funded partnership awards with China and Japan, collaboration awards with Brazil and Malaysia, and a steady influx of international PhD students who join the MIB and the University of Manchester. Further information about the Centre and routes to collaboration can be obtained from the SYNBIOCHEM website: http://synbiochem.co.uk.

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