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Designer microbes for biosynthesis

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Microbes have long been adapted for the biosynthetic production of useful compounds. There is increasing demand for the rapid and cheap microbial production of diverse molecules in an industrial setting. Microbes can now be designed and engineered for a particular biosynthetic purpose, thanks to recent developments in genome sequencing, metabolic engineering, and synthetic biology. Advanced tools exist for the genetic manipulation of microbes to create novel metabolic circuits, making new products accessible. Metabolic processes can be optimized to increase yield and balance pathway flux. Progress is being made towards the design and creation of fully synthetic microbes for biosynthetic purposes. Together, these emerging technologies will facilitate the production of designer microbes for biosynthesis.

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Introduction

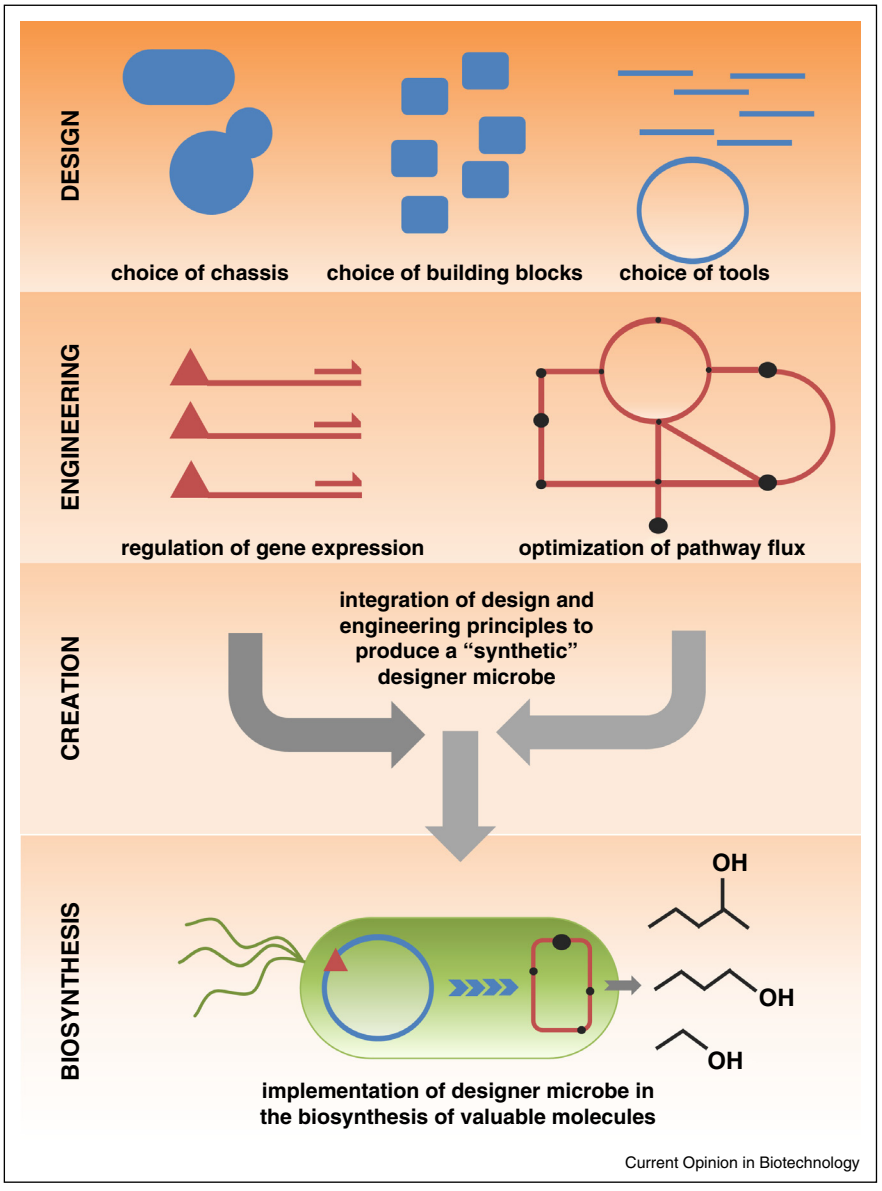
Imagine a world where microbes produce the electricity that lights our homes and schools, the fuel that runs our cars, the pharmaceuticals that keep us healthy, and the foodstuffs that we eat. While such ideas may sound far-fetched, many of these applications are already in existence, or are within our reach [1–4]. Microbes are a useful platform for the biosynthesis of desirable products, evidenced by their long history of adaption for the food and pharmaceutical industries. Microbes grow quickly on relatively cheap carbon sources, culture size can easily be increased to scale up production, and the naturally occurring metabolic processes of microbes can be harnessed to produce significant quantities of useful compounds [5]. It is therefore unsurprising that both microbial primary metabolites (e.g. vitamins, nucleotides, ethanol and organic acids) and secondary metabolites (e.g. antibiotics, cholesterol lowering compounds and anti-tumor compounds) have a global market value of several billion dollars [6].

Yet, microbial industrial biotechnology has not been without its drawbacks. Traditionally, the yields and repertoire of products were limited to the natural capacity of the existing microbial biosynthetic pathways. This problem has partially been addressed by exploring microbial diversity to find other species that have evolved to become more efficient at producing a particular target compound, or different compounds [7]. However, laboratory conditions for the cultivation of the newly discovered microbes often require extensive optimization, and the characterization of the biosynthetic pathways responsible for producing the metabolites of interest is a time-consuming process. Therefore, these measures have only provided a temporary stopgap solution to the challenge of being able to fully manipulate the biosynthetic output of a broad range of desirable and valuable products on demand.

With the dawn of the post-genomics era came a revolutionary change in the way that we understand and view microbial biosynthetic pathways [8]. An exceptionally large amount of microbial genome information is available via databases such as NCBI (http://www.ncbi.nlm.nih.gov/genomes/MICROBES/microbial_taxtree.html), GenomeNet (http://www.genome.jp/), and JGI (http://genome.jgi-psf.org/). Together with our biochemical knowledge of enzyme function, and our ability to synthesize DNA from scratch, we have a powerful toolset for the discovery and design of new biosynthetic networks [9]. The last decade has seen incredible advances in our ability to tailor microbial enzymes and metabolic processes for our purposes, thanks to developments in the fields of metabolic engineering, enzyme evolution, and synthetic biology [10••,11,12]. Now, we can program microbial factories by combining diverse enzymes in a heterologous host to produce compounds that were previously unattainable [13]. Novel and pre-existing metabolic pathways can be optimized by mediating strict control over the expression of the encoded pathway enzymes, as well as by engineering the enzymes to improve efficiency [14]. We even have the capability to create beyond that which is provided by nature with the advent of techniques such as *de novo* engineering of enzymes to carry out unnatural reactions [15], and the construction of bacterial cells with minimal and synthetic genomes [16••].

In this opinion we discuss the process of designing and engineering a microbial system for the biosynthesis of

Figure 1



A schematic representation of the design and engineering of a microbe for biosynthesis. The design of a microbe for a particular biosynthetic purpose involves selection of appropriate chassis, building blocks, and DNA assembly tools. The designed microbe can then be engineered with these components. Optimization of the biosynthetic system occurs by regulation of gene expression, and metabolic flux improvement via network modelling, spatial organization and protein design. The integration of these principles and improvements can result in a tailor designed biosynthetic scheme for the high level production of valuable compounds.

desirable compounds (Figure 1). Some of the most recent tools and technical advances are presented, and a few key examples are used to highlight successes and important design principles to take into consideration (Table 1). While not an exhaustive review, this paper will serve as a general 'roadmap' to introduce readers to some of the most up-to-date trends in the production of designer microbes for biosynthesis.

Designing a microbe for biosynthesis

Choice of chassis

The choice of chassis, or microbial host, for biosynthetic production is dependent on the tractability of the organism. It is usual to select a microbe that can be easily cultured, that has a known genome sequence, that is amenable to genetic manipulation, and that has well understood metabolic pathways. The model organisms