Editor's LETTER

ACS chemical biology

Synthetic Science: Assembly Required

In this time of making resolutions and setting priorities for the new year, our Review issue is focused on a field that is driven by goals—synthetic biology. Synthetic biology researchers are interested in both the construction of new biological components and systems and the reconfiguration and modification of existing biological components and systems. These efforts were first classified as "synthetic biology" in 1974 by my prescient colleague Waclaw Szybalski. Szybalski noted that once the fundamental units of biology are known, they can be used to synthesize new systems (from pathways to organisms). This view emphasizes that, like synthetic chemists, synthetic biologists are target-oriented. The exploitation of building blocks to generate larger and more complex targets is a strategy common to both fields. While chemists use covalent interactions to assemble their targets, synthetic biology relies upon noncovalent interactions. For more than 150 years, chemists have been elucidating the rules for covalent bond formation, and the subject remains an active area of investigation. Given that our understanding of noncovalent interactions is far less advanced, how can a synthetic approach be based upon it? The Reviews in this issue address this question by outlining examples, strategies, tools, and new directions for synthetic biology.

Building blocks that can be used to construct molecular assemblies are the focus of the Reviews by Chow *et al.* and Woolfson and coworkers (*1*, *2*). The former focuses on the chemical synthesis, and subsequent incorporation, of modified nucleotides into RNA. Non-natural RNA derivatives can be used to engineer new or improved functions that are inaccessible when only standard nucleotides are used. Moreover, there are hundreds of natural modifications with unknown function, and access to synthetic modified RNAs can facilitate the creation of a complete registry of RNA components for synthetic biology. With a complementary set of building blocks, Woolfson and colleagues describe the utility of peptides in synthetic biology. The authors delineate various hierarchical degrees of complexity that give rise to self-organized functional biological systems. They provide specific examples of peptide design using α-helical coiled coils as basic components and explain how these strategies can be used to construct assemblages of novelty and complexity.

As described in the first two Reviews, the building blocks for synthetic biology can come from chemical synthesis. Cells too provide convenient and renewable sources of molecules. Cells can be modified so that endogenous cellular pathways are co-opted for new purposes. When an artificial process is engineered in a cell, however, the cell must retain its own metabolism to survive. Filipovska and Rackham discuss this and related issues in their Review on building a parallel metabolism (*3*). The authors describe how modules, discrete entities with a single biological function, can be insulated from each other. They further delineate how parallel pathways can be evaluated and optimized by methods such as genetic screening and selection. They highlight the utility of orthogonal modules and describe how this approach has been used to re-engineer translation and the genetic code.

The Review by Jay Keasling illustrates and underscores the benefits of using cells as renewable sources of molecules (*4*). He describes the advantages of engineering metabolic pathways to afford desirable compounds. He contends that chemists, biologists, and engi-

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Editor's LETTER

neers can more effectively revamp or build biological systems from scratch if they employ standardized parts. For example, a catalog of well-characterized biosynthetic components provides the means to design, test, optimize, and implement integrated large-scale biosynthetic units. An illustration is provided of how these principles can be used to engineer production of the antimalarial drug artemisinin. This example highlights the common goals but complementary approaches of synthetic biology and synthetic chemistry.

Advocates of synthetic biology are using it to address global problems. The Keasling Review illustrates its utility for producing therapeutics that target key infectious diseases. In an In Focus commentary, Pamela Silver offers a view of the promise of synthetic biology for energy production (*5*). She outlines recent efforts to convert biomass into fuels—including ethanol, butanol, biodiesel, and hydrogen—and the challenges that lie ahead in making these viable options. In additional commentaries, Jay Keasling and Hans Blaschek describe large-scale research initiatives at the University of California, Berkeley, and the University of Illinois directed toward developing and refining strategies for biofuel production (*6, 7*).

Together, the publications in this issue emphasize that advances in synthetic biology depend upon understanding how biological building blocks function and how to put them together. As mentioned, the emphasis on constructing new assemblages from component parts is shared with synthetic chemistry. Many strategies (*e.g.*, elucidating and optimizing the rate determining step in a process) are shared between the fields. A dialog between chemists and biologists can facilitate advances on all fronts.

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