Building up biology

A collection of articles illustrates ways that synthetic biology tools and tactics both draw from and stimulate chemical biology research.

In 2005, Thomas Knight declared that "biology will never be the same" in describing research from Drew Endy and colleagues that extended engineering terminology such as 'refactoring' and 'parts' to a biological context (*Mol. Syst. Biol.* **1**, 2005.0020, 2005). By then, Elowitz's and Leibler's foundational 'repressilator' study, in which three transcriptional repressors were integrated into an artificial biological clock, was five years old (*Nature* **403**, 335–338, 2000) and the term 'synthetic biology' was already in use. But the collusion of major improvements in DNA sequencing and synthesis with this new linguistic framework did launch a transformation in the way biological systems are studied and manipulated that continues today. Like chemical biology, synthetic biology evolved in a technology-focused and highly interdisciplinary milieu. Though the disciplines had different origins, synthetic biology and chemical biology share overlapping aims such as testing and extending our understanding of biological systems and making tools to manipulate biomolecules, cells and organisms. This conceptual intersection is highlighted by a collection of pieces published in this issue.

The scientific literature and synthetic biology–related websites are replete with efforts to define synthetic biology. Some insist synthetic biology is focused solely on the development and standardization of parts, whereas others take a more holistic view, including topics such as protein design, metabolic engineering and the minimal cell. These divergent views are not unexpected, according to Kristala Prather, who suggests, "if you ask five people to define synthetic biology, you will get six answers" (*Nat. Biotechnol.* **27**, 1071–1073, 2009). Perhaps synthetic biology and chemical biology are alike in that the fields are defined more by the overall mindset and approach of the researchers involved rather than by any particular scientific theme or biomolecule; indeed, the Synthetic Biology Engineering Research Center defines synthetic biology in part according to the 'intellectual agendas' contributing to the field (http://www.synberc.org/what-is-synbio/).

Regardless of the exact definition, synthetic biology is perhaps best known for the creation of parts and devices that may control gene expression or integrate signaling pathways. In this vein, Motta-Mena *et al.* report a new minimal optogenetic gene expression system based on a bacterial LOV domain (p. 196). This system offers improved performance for light-controlled transcription and represents a case where chemical biology research, having defined the mechanism of the Lov protein family, can be quickly adapted to optimize a synthetic biology system. In their research, Gaber *et al.* use transcription activator–like effectors (TALEs) to construct biological counterparts of all two-input logic gates in human embryonic kidney cells (p. 203). As TALEs bind DNA using a programmable amino acid code, these circuits could lead to more extensive orthogonal regulatory networks.

Synthetic biologists have been proficient in translating basic biological insights into applications-oriented engineering methods. For example, phage-assisted continuous evolution (PACE), in which proteins can be evolved for a new function with minimal human intervention, combined the power of exploring sequence space broadly while limiting characterization required (*Nature* **472**, 499–503, 2011). Carlson *et al.* now improve on this method by adding negative selection to diminish the original enzyme function as the new activity evolves and stringency modulation to enable evolution of functions that are not present in the parent sequence (p. 216). In their study, Ravikumar *et al.* drew inspiration from a replication system from *Kluyveromyces lactis* to create an entirely different method for protein engineering in which continuous evolution of a cytosolic gene occurs while the host genome is unaffected (p. 175). Finally, basic biology was translated to application more than two decades ago in the insertion of unnatural amino acids at amber stop codons, a technique that has been used to create a wealth of modified proteins. Ryan Mehl now seeks to make this technology more accessible in the creation of the first Unnatural Protein Facility (p. 167).

Robust engineering strategies also allow synthetic biologists to explore basic questions in biology. For example, Hammerling *et al.* now examine the evolution of phage propagated with an *Escherichia coli* host that efficiently incorporates an unnatural amino acid (p. 178). Their discovery that phage can accumulate beneficial mutations without selective pressure to make use of a twenty-first amino acid provides unexpected insights into genetic code evolution. More broadly, O'Donoghue *et al.* recently highlighted several aspects of translation that remain underexplored in developing an understanding of amino acid usage (*Nat. Chem. Biol.* **9**, 594–598, 2013), suggesting fertile ground for chemical and synthetic biologists alike.

The papers above highlight some of the scientific overlap between chemical biology and synthetic biology. However, these articles by no means represent the full scope of synthetic biology research welcome at *Nature Chemical Biology*. We take an active interest in papers that describe new ways to approach challenges in the field, such as bypassing extensive protein engineering by scanning the growing genomic data to identify orthogonal enzymes (*Nat. Chem. Biol.* **10**, 99–105, 2014). We encourage submission of manuscripts that build on existing mechanistic understanding of biological systems to create new tools and parts (*Nat. Chem. Biol.* **8**, 447–454, 2012) or to enable practical applications in human health and metabolic engineering (*Nat. Chem. Biol.* **8**, 527–535, 2012). Finally, we view applications of synthetic biology methods to investigate complex biological phenomena in a rigorous and defined way (*Nat. Chem. Biol.* **5**, 929–935, 2009) as an exciting intersection between the fields.

Beyond overlapping scientific interests, chemical biologists can be inspired by the 'open science' mentality and intellectual play inherent to synthetic biology, exemplified by the registry of parts and undergraduate competitions that bring the imaginative ideas of young scientists to an international stage. By considering when and where defined parts might be employed, chemical biologists can also leverage the skills of synthetic biologists—in the form of programmable devices—to enable new functional insights. Indeed, a central theme at the First International Mammalian Synthetic Biology Workshop (http://mammalian-synbio.org/) was to identify 'application pulls', or potential applications or open biological questions that could drive the development of synthetic biology methodology. Thus, increased communication across fields can only serve to build up new opportunities for chemical and synthetic biologists.