Progress in Engineering Synthetic Cells and Cell-Free Systems

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Editorial

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What defines life, and how do living systems distinguish themselves from nonliving entities? Can life be fabricated from inert molecules? Those questions have been driving the rapid growth of a new area of synthetic biology: a groundbreaking scientific field centered on the construction of synthetic cells. This ambitious initiative aims to uncover deep insights into the fundamental principles of life, and holds the potential for numerous practical applications.

Over the past two decades, significant efforts have focused on the assembly of biological cells: as a tool to uncover the underlying physical and chemical processes that drive cellular functions as well as to harness cellular functions for applications in chemistry, medicine, and sustainability. From the assembly of biological components (ribosomes, polymerases, etc.) that harness the chemical activity of cells to the assembly of amphiphilic and biopolymeric components (lipids, cytoskeleton, disordered proteins, etc.) that mimic the structural features of cellular matrices and compartments, the functional and structural features of biological cells have inspired new methods and new materials to both interrogate and harness biological design principles. Constructing a living cell from molecules in the laboratory offers a groundbreaking opportunity to address these goals, while simultaneously transforming our understanding of life.

This virtual special issue on progress in the field of synthetic cell engineering covers new tools for the design of cell-free systems, investigates the bidirectional relationship of biochemical reactions, cellular compartments, and biological processes, and provides new methods to evaluate synthetic cell functions. The collection of papers highlights new directions in the field of synthetic cell design, and an exciting educational initiative that centers on the design and evaluation of synthetic cell curriculum (DOI: 10.1021/acssynbio.3c00275).

One overarching theme of this issue is work to enhance the capabilities of cell-free systems, platforms that recapitulate the biosynthesis and biochemical reactions of the cell. Seo and Ichihashi explored how non-protein factors impact DNA replication, transcription, and translation (DOI: 10.1021/acssynbio.3c00130). Work by the Adamala lab characterizes a new fluorescent protein, *Aequorea* proteins from jellyfish, a novel family of fluorescent proteins used in cell-free systems, that adds to the toolbox of available reporters for engineering complex genetic circuits (DOI: 10.1021/acssynbio.3c00057). The Kanamori lab describes the design of a new cell-free method to conduct N-terminal acetylation and myristoylation of newly synthesized proteins in vitro, offering a useful strategy for post-translational modification of proteins in vitro (DOI: 10.1021/acssynbio.3c00191). The Banta lab introduces an ATP-regenerating enzymatic cascade that uses enzymes in the NPD(P)(H) cycle and that should improve the efficiency of cell-free reactions by limiting the need for phosphate donors (DOI: 10.1021/acssynbio.3c00172). Wang et al. demonstrate the synthesis of Fe−S clusters, essential cofactors in many biocatalysis processes. This work expands the functionalities possible to reconstitute, and study, in cell-free systems (DOI: 10.1021/acssynbio.3c00155). Signal amplification, a perennial challenge in all biological systems, can be improved with conversion from "analog" biological output to "digital" binary readout (DOI: 10.1021/acssynbio.3c00227). Finally, work led by the Huck and Sandoval groups harness new types of cell-free systems from a near- minimal synthetic bacterium (DOI: 10.1021/acssynbio.3c00114) and genetically modified *E. coli* (DOI: 10.1021/acssynbio.3c00239), respectively.

Compartmentalization plays an integral role in cells, spatially segregating biochemical reactions and regulating cellular movement and shape changes. Several papers in this issue explore compartmentalization in one way or another: Fink et al. present a minimal model system consisting of actin in giant unilamellar vesicles and adhered to different micropatterned surfaces to study the contributions of actin polymerization and membrane adhesion on vesicle shape (DOI: 10.1021/acssynbio.2c00516). In another investigation on cell shape changes, the Campillo group presents a system that localizes actin polymerization to membrane domains and how actin can induce membrane deformation and/or reorganize lipid domains (DOI: 10.1021/acssynbio.3c00268). Biomolecular condensates are another type of compartment that has generated interest across disciplines. Work by the Huck group and Bajaj group explore how condensates impact cell-free reactions (DOI: 10.1021/acssynbio.3c00069) and how they can be reversibly assembled within lipid membranes (DOI: 10.1021/acssynbio.3c00249). The Hansen lab tackles an ongoing problem in biological reactions that have a limited number of reactants: noise. By encapsulating a bacterial cell-free gene expression system in water-in-oil droplets, they show they can reduce gene expression noise greater than 2-fold than the unencapsulated system (DOI: 10.1021/acssynbio.3c00174).

Yet another theme of this issue is the development of new tools and methods to study minimal cellular systems. Kaufmann et al. show how polymer microgels provide a useful platform to analyze protein−DNA interactions that regulate bacterial cell division (DOI: 10.1021/acssynbio.3c00488). Improved methods of high-throughput sorting of synthetic cells (DOI: 10.1021/acssynbio.3c00074) opens up possibilities for artificial evolution experiments to further increase complexity of those systems. Finally, Lavickova et al. introduce a microfluidic system that allows for continuous dialysis of low molecular weight proteins and allows for extended durations of cell-free reactions with corresponding greater yields of proteins (DOI: 10.1021/acssynbio.2c00453).

Some of the most important driving forces in our field are practical applications. Examples of biomedical applications of synthetic cell technologies demonstrated in this collection include neutrophils analogues (DOI: 10.1021/acssynbio.3c00309), bacteriophages (DOI: 10.1021/acssynbio.3c00239), SARS-CoV-2 particles (DOI: 10.1021/acssynbio.3c00133), and peptide hormones (DOI: 10.1021/acssynbio.2c00680). A review summarizes progress in artificial tissue engineering (DOI: 10.1021/acssynbio.3c00061), including progress toward potential clinical applications.

This issue contains several perspectives on the field: Bailoni et al. review design strategies for a minimal metabolism that would bring us closer to the goal of complete artificial cell (DOI: 10.1021/acssynbio.3c00062). Shrivastava et al. review molecular mechanisms that support artificial cell motility (DOI: 10.1021/acssynbio.3c00271). Partipilo et al. discuss important considerations around electron carriers and reductive redox reactions that are needed to drive metabolic reactions in a synthetic cell (DOI: 10.1021/acssynbio.3c00070). Lin et al. consider a structural hurdle in the field of synthetic cells, mainly the construction of synthetic tissues from synthetic cells (DOI: 10.1021/acssynbio.3c00061).

Our century is often referred to as “the century of biology”. Advances in engineering new biological chassis by building cells from the bottom up is one of the driving forces of making this a reality that benefits us all.

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