Editorial

Special Issue – Synthetic Cell Biology

Cell Biology 2.0

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'*Verum esse ipsum factum*', the true is in the made – Giambattista Vico

Synthetic Cell Biology sounds intriguing, but the name begs the question – why should we try to rebuild or reprogram the cell, especially when we barely understand how cells work? This issue of *TiCB* explores this emerging area in which scientists are taking apart, rebuilding, reprogramming, and repurposing parts of the cell. The reviews cover a wide range of scales, from microscopic molecular machines to macroscopic, multicellular tissues. These reviews highlight the fact that, in addition to its role in harnessing and unleashing the power of cells for new and future applications, synthetic biology also has an important role to play in facilitating the understanding of complex cellular processes. In short, we can learn much about cells through the process of trying to build them (or parts of them). And if we understand cells, we can start to really harness their power.

Cell biology has historically been primarily an observational science, inextricably linked with tools like the microscope, which first enabled humans to peer into the remarkable world of the cell, with its diversity of forms and complex and dynamic inner structure. Yet today, even as we know the genomic parts list of the cell, we realize that there is a huge gap in our mechanistic understanding of the logic of how these systems work. On the one hand, we can observe these beautiful systems that yield complex cellular structures, movements, and regulatory decisions; on the other, we have a list of molecular parts that somehow underlie these behaviors and decisions. But the middle ground linking how these parts fit together and work as a system is often missing. We have a serious gap in the mesoscopic mechanistic understanding of how microscopic molecules work together to yield complex macroscopic behavior.

Synthetic biology as applied to cell biology can help to address this gap, because in many ways it is a philosophical descendant of old-school reconstitution biochemistry. It offers a unique and powerful way to construct simple, stripped down, and manipulable molecular systems, which can then be used gain insight into the fundamental rules of how some complex biological process takes place. But now, thanks to the power of genetic engineering, much of this manipulation and perturbation of systems can take place in the milieu of the living cell, with its basic metabolic and transcriptional systems and complex spatial environments. The cell, or even artificially constructed cells, can serve as the new test tube for logical and systematic analysis of a process. As Vico first suggested (and Richard Feynman later reiterated), if we can build it, we can understand it.

Predictive, mechanistic understanding of how the parts of a cell work together to generate cell behaviors is not only interesting in its own right; it would provide a rational basis to turn cell biology into an engineering discipline. Synthetic cell biology has the promise of remarkable biotechnology applications. Many advances have been made in harnessing cells to create new and useful molecules, by cobbling together new strings of metabolic enzymes. But in many ways, this is only the tip of the iceberg of what cells could do. Current efforts have largely ignored the cell, its structure and regulation, as a tool to harness. Cells are some of the most powerful and capable devices we know, especially in producing complex products. Manipulation of cellular organelles, transport systems, and secretion systems and their regulation could, if properly applied, have dramatic effects on cell-based production of fuels, drugs, nutrients, and chemicals. Ultimately, learning how to reprogram the machinery of the cell extends far beyond biofermentation – it may lead to dramatic advances in designer cells (or cell-inspired devices) that can execute precision therapeutic or regenerative functions. It may even be possible to create new cells that have hybrid functions and structures that are completely novel. The next few decades offer tantalizing promise of how our understanding of cell biology could be applied, and it is time for cell biologists to start thinking creatively about how cells as machines could be harnessed.

The reviews in this issue cover several fundamental issues. Thery, Schwille, and Odde discuss different ways that reconstitution or synthetic approaches can be used to understand the fundamental problem of self-organization – how molecules dynamically interact with one another to yield higher-order structure systems such as the cytoskeleton and the cell division machinery. Odde explores how cellular processes can be reconstituted or visualized using dancers as a medium.

Maharbiz and Gartner explore the intriguing problem of multicellular assembly, which is intimately linked to developmental biology. Can we understand the rules of

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how molecular systems can lead to hierarchical assembly of multicellular structures like tubes and spheres and eventually into complex tissues? How might we manipulate this to gain a better understanding, and is it eventually possible that we can build novel and arbitrary macroscopic structures from reengineered cells?

Bathe, Yeates, Reck-Petersen, and Silver explore different ways in which we can harness and repurpose the machinery of the cell. Bathe explores the diversity of ways in which nucleic acids, with their simple Watson–Crick base pairing can be used as a substrate to build complex assemblies, carry out catalysis, and build information-processing systems. Yeates explores the way in which known protein modules can be used to build novel assemblies. Reck-Petersen discusses how we can harness the power of cytoskeleton-based transport machines, and Silver reviews progress towards harnessing cellular compartmentalization for metabolic engineering.

These articles underscore the promise of synthetic cell biology, both as an engineering discipline and as an alternative route to understanding the secret of how cells work. But this issue is not so much a roadmap, as an invitation to participate. Figuring out how to reimagine the cell biology of the future is left as an exercise for the reader.