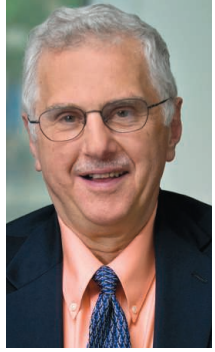

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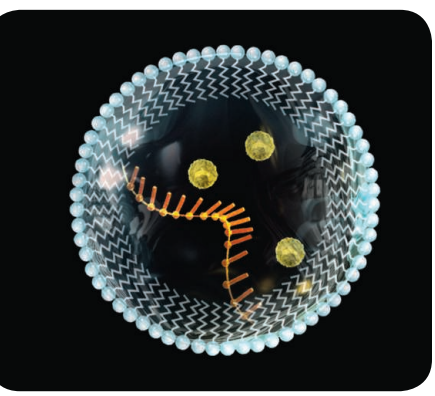
A Grand Challenge in Biology

RICHARD FEYNMAN, A BRILLIANT NOBEL PRIZE–WINNING PHYSICIST, IS OFTEN QUOTED FOR his statement that "What I cannot create, I do not understand." The remarkable advances in our knowledge of the chemistry of life achieved in the past few decades, published in *Science* and many other journals, could lead nonexperts to assume that biologists are coming close to a real understanding of cells. On the contrary, as scientists learn more and more, we have increasingly come to recognize how huge the challenge is that confronts us. In this special issue, we review the progress made in the decade-old field called synthetic biology, which, as Feynman would advocate, creates biological networks in order to help us understand, and in some cases redesign, living systems. Along with its promise for the biotechnology industry, synthetic biology has the potential to become a powerful new tool for the long-term fundamental research needed to more effectively create breakthroughs in improving human health and welfare and the environment.*



Why do we need this basic research aimed at attaining a deep understanding of the chemistry of life? A complete catalog of the tens of thousands of different molecules present in a human or mouse cell, along with a map of their myriad mutual interactions, is likely to be obtainable with the wide variety of different techniques that are now available. But how can we make sense of such enormous chemical complexity? There are about 21,000 distinct proteins encoded by the human genome. At present, one can only guess the function of nearly half of these gene products. And even when we know the exact function and structure of a particular protein, embedding this protein in the cell often reveals a network of interactions so complex that the biological outcome of any perturbation, such as a drug treatment, is unpredictable. Clearly, there is an enormous amount left to learn.

Fortunately, many living cells are much less complicated than the cells of mammals. Because all living things on Earth are related through evolution, one can bootstrap one's way to understanding human cells by discovering how simpler cells and organisms work. A detailed study of *Mycoplasma genitalium,* a tiny bacterium that causes human disease, suggests that it can grow and divide with a minimal set of only about 430 genes. But no function can thus far be assigned to about 100 of its essential proteins.† This suggests that we may be largely ignorant of some critical functions of proteins, such as their roles in the exquisite spatial organization of the molecules inside cells.

In 1945, the pioneering physicist Max Delbruck started the "phage course" at Cold Spring Harbor Laboratory to recruit a group of talented scientists to work on bacterial viruses. This was the start of modern molecular biology, and it led to remarkable breakthroughs in our understanding of the then-mysterious molecular basis of heredity. Today, we need a focus on producing cooperative groups of scientists who aim at a complete understanding of the simplest free-living cells. Progress is being made.‡ But many more biochemists must get involved in order to reconstruct with purified components the different interacting protein assemblies—the subsystems in cells—so as to elaborate their detailed chemistry. We will also need synthetic biologists to dissect these subsystems, both by rewiring them and by the creation of functions through their transplantation to new settings. And biologists will need the help of mathematicians, computer scientists, and engineers to make sense of the enormously complicated network of molecular interactions found in even the least complex living cells. To make all this possible, governments and foundations must become much more imaginative in allocating resources for the long-term fundamental research needed to prime major breakthroughs in human health and global sustainability.

– Bruce Alberts

10.1126/science.1213238

*N. Nandagopal, M. B. Elowitz, *Science* **333**, 1244 (2011); W. C. Ruder, T. Lu, J. J. Collins, *Science* **333**, 1248 (2011).
†J. I. Glass *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **103**, 425 (2006). ‡For example, see S. Kühner *et al.*, *Science* **326**, 1235 (2009).

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