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THE FUTURE POSTPONED

Why Declining Investment in Basic Research Threatens a U.S. Innovation Deficit

Illustrative Case Studies

A Report by the MIT Committee to Evaluate the Innovation Deficit

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SYNTHETIC BIOLOGY

Redesigning life itself in the lab, and in the process potentially transforming bio-manufacturing, food production, and healthcare.

Suppose that it was possible for biological engineers to create living cells designed for specific purposes as easily as tech engineers now create new digital circuits and the software to run them? Suppose scientists could program bacteria, plants, or even human cells to make them more productive or cure disease? In fact, the beginnings of just such a revolution in the field called synthetic biology is well underway. And once developed, the techniques for designing and altering the DNA found in every living cell, such that genes can be turned on or off at will or altered in useful ways, are relatively easy to apply: this year some 2300 high school and college students from around the world participated in an international synthetic biology competition to program biological circuits in novel ways.

Just as with the IT revolution, synthetic biology started by designing simple circuits, such as on/off switches, for the DNA in bacterial cells. Then they built more complex circuits, including ways for living cells to communicate with each other and methods (analogous to software programs for biological circuits) to orchestrate the behavior of whole groups of cells in a variety of organisms—yeasts, plants, and mammalian cells. To do this requires understanding in detail exactly how DNA behaves and then ensuring that engineered circuits also do exactly what they are intended to do. But what has facilitated progress is that the mechanics of how DNA functions in a cell and the interactions between genes, proteins, and other cellular constituents is remarkably similar across species. In particular, all DNA contains sequences of the same four nucleotides. Some of these sequences are the genes that guide synthesis of proteins, and others are "promotor" sequences that turn neighboring genes on and off. And biological engineers have learned how to control the promotors, in turn, by using the fact that there are specific proteins that bind to them.

The process of designing biological circuits and thus programming biological functions first at the cellular level and then in ways that affect the entire organism is still difficult and labor intensive, in part because there has not yet been enough investment in automating the toolset. Experiments involve a few cells at a time, not billions of cells. By the same token, large-scale industrial applications of synthetic biology are still in the future—even though the potential markets in bio-manufacturing, in food production, and in healthcare might easily exceed the size of the technology market. Nonetheless, the field is making progress, developing cellular sensors and actuators and learning how to organize the logic operations of

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biological circuits within a cell—technologies that are the equivalent of USB connectors and integrated circuit chips in the tech world. What this means is that synthetic biologists can now begin to take circuit elements and easily plug them together to create the genetic behavior they desire.

Moreover, the toolset is not likely to be limited to the DNA and genes that nature has created. Just last year, researchers in California engineered a bacteria by inserting two new, synthetic nucleotides in its DNA—in effect, adding two new letters to the genetic alphabet and potentially expanding the chemistry of life. That gives biological engineers yet more flexibility to construct altered genes and designer proteins and thus program cells to operate in new ways, or to create novel catalysts and materials.

What might the synthetic biology revolution make possible? One likely application might be to create a kind of super probiotic able to identify and kill harmful bacteria in the stomach by sensing specific molecules they secrete. Another possibility stems from a recent discovery of biomarkers that identify a cancer cell; with a list of such biomarkers, it should be possible to engineer a virus with the circuitry to identify cancer cells, enter them, and direct the cancer cells DNA to produce a protein that will kill them—irrespective of the type of cancer. As synthetic biology research in mammalian cells expands, it seems likely that it will be possible to largely eliminate animal testing for new drugs and even to regenerate new organs. Eventually, treatments for many health conditions that have genetic origins, customized to the individual, might be possible, since it is far easier and faster to engineer a virus to turn off a bad gene than it is to develop a new pharmaceutical drug. Engineering yeast or algae to produce foods or other biomaterials is likely to become an even larger industry than it already is, manufacturing far more complex materials. There is clear potential to create climate-friendly fuels and engineered plants or bacteria to restore degraded environments. The fundamental knowledge and the toolset needed is common to all these applications—and manipulating DNA to control living cells is potentially far easier than traditional drug development or chemical synthesis of materials.

Indeed, so powerful is this approach that synthetic biologists are already developing ways to consider in advance what could go wrong or how an innovation could be mis-used—in effect, to de-risk innovations before they happen. That can't completely guarantee against future mis-use, but since the technology is

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already widespread, it's clearly important that the U.S. have the capacity to identify harmful uses and quickly develop countermeasures. Yet while US research agencies debate how—and which agency—will fund this new field, research in synthetic biology is expanding very rapidly internationally, especially in Europe, in Latin America, and in Asia; China and half a dozen other countries have already launched national initiatives. One measure of the innovation deficit is that—even though the synthetic biology revolution began in the U.S.—student teams from this country have failed to win the international synthetic biology competition in 8 of the past 9 years, in part because of a lack of laboratory facilities. That same lack impedes research progress as well. And what is at stake—leadership or at least a competitive role in a transformative new technology—is far more important than a student competition.

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