PRESIDENTIAL ADDRESS

Meeting global challenges: Discovery and innovation through convergence

Integrate biology, physics, engineering, and social science to innovate

By **Phillip A. Sharp**

Our awareness of the global nature of major problems facing our planet is relatively new and demands global responses for which neither the scientific community nor the general public is well prepared. To meet such global challenges requires the engagement of people and their leaders from diverse cultures and experiences. While many sectors of society must become involved, the scientific community has a special role in preparing for these challenges. It is impossible to consider here all of the roles of scientists and engineers in this transformation, whether advancing knowledge of nature, translating new insights into innovations, or educating future generations. But few would disagree that in the long term, discovery and innovation are central to effectively meeting these challenges. Yet it is often difficult to link discovery and innovation to their impact because of the years of development required before a discovery matures to a level that can be adopted on a global scale. I highlight below how some organizations are planning to accelerate the transition from discovery to innovation to address some of the great challenges facing society. As an illustration, I discuss the history of the transition from discovery to innovation at the molecular level in life sciences. At the end, I comment on how further convergence of physical, mathematical, engineering, and social sciences with life sciences will accelerate innovation.

The world will be considerably changed by mid-century, but in ways not yet fully clear. Within the lifetime of our children and grandchildren, Earth will have around 9 billion inhabitants, and each person will need to be fed from a square of arable land about 130 meters on each side (*1*). Inequities in standards of living between developed and many underdeveloped countries will continue to diminish as the result of modern trade policies and technology, increasing demand for food, energy, and better health care. Increasing connections across the global economy and the expansion of knowledge capital are driving a wave of global entrepreneurs, with emerging nations like India and China showing how innovation-based growth can enable the movement of hundreds of millions of people into the global middle class. But as the world is calling for more consumption, we are facing global warming, with increasing accumulation of heat-retaining gases and further stress on environments.

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DISCOVERY AND TECHNOLOGY, ENTREPRENEURSHIP, AND INNOVATION

Society probably has never been more uncertain about the prospect of a better future. While scientific discovery and technological innovation have enabled innumerable advances, many view the global challenges facing us as products of past advancements in science. It is true that scientific advances and the innovations and corresponding economic growth they have generated are contributors to the global climate challenge we must now overcome. This climate change is connected to, and can increase, the challenges of poverty and disease. In spite of these concerns, innovation-based growth that will enable the movement of hundreds of millions into the global middle class is a given with which we must wrestle. These facts have led to some skepticism in the developed world about whether continued advancement of technology will contribute to a better future.

I believe that some of the concerns about applications of advances in life sciences, such as the adoption of genetically modified organisms (GMOs) and other new technologies, have their source in this skepticism. But I am more convinced than ever that the only avenue to a better future is continued advancements of science that are wisely applied to society. Science-based innovation is tied to the problem, but it is also central to the solution.

Discovery and innovation are means by which science can affect society. But it is important to recognize that innovation is not solely the discovery of new knowledge or the invention of new materials, processes, or devices. The National Innovation Initiative that led to the America Competes Act has a useful definition: Innovation is the "intersection of discovery, invention and insight leading to the creation of social and economic value." The connection between discovery and economic growth has never been more apparent. It is widely accepted that innovation is at the heart of economic growth, accounting for approximately half of its expansion over the past 50 years (*2*). This relationship drives much of the public interest in funding science and the education of students in many nations, which increases the capacity to solve global problems.

The "classical" view in the process of translating science and technology for society is that scientists "discover," engineers "invent," and entrepreneurs "innovate." In the past, scientists viewed these three stages as belonging to properly separated worlds. Vannevar Bush's 1945 treatise *Science: The Endless Frontier*, which led to the creation of our modern research universities, argued that basic research was the "pacemaker" of technological advance, and therefore investment in research would inevitably yield innovation.

True enough, but to be efficient, the process requires great attention and nurturing. Historically, many universities have had faculties of scientists and engineers with

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Cluster of high-tech companies near MIT

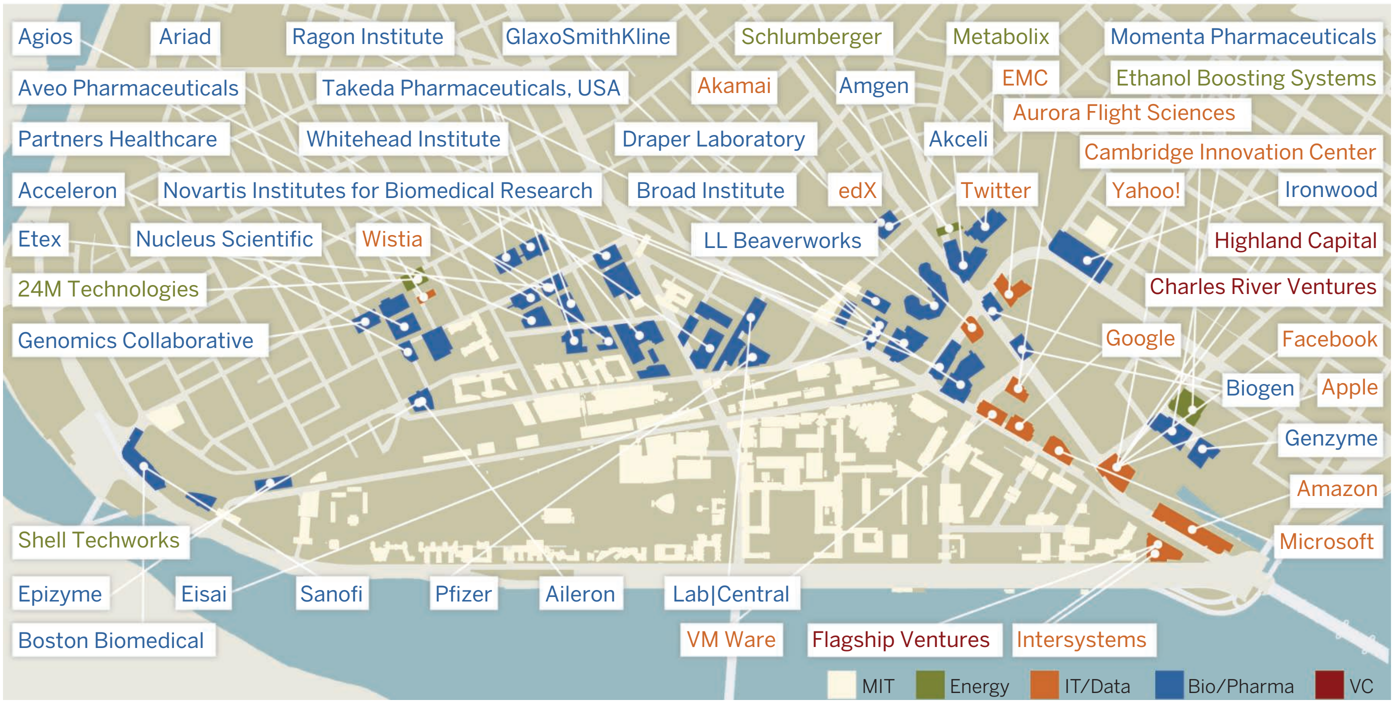

Fig. 1. Cluster of high-tech and related organizations on the boundaries of MIT (source, MIT).

the objective of integrating discovery and invention and educating students in both activities. However, the presence of entrepreneurs on many campuses and the education of students in this subject are recent developments. For example, Ed Roberts of the Massachusetts Institute of Technology (MIT) notes that historically, a third of all MIT alumni have started companies over their 30- to 40-year careers (*3*). The surprising change in the past decade is that now a third of MIT alumni start companies within 10 years of leaving the campus. Recent graduates of other universities both here and abroad are also engaging in such entrepreneurial activities. In many cases, these startup companies integrate skills that accelerate innovation by combining discovery, invention, and entrepreneurship into a team. Recently, Rafael Reif, president of MIT, suggested an educational need to expand these experiences from alumni to students in science and engineering. This interest in integrating entrepreneurship with training in technology further highlights the relationship between discovery and the economy and the willingness of many public and private research institutes to contribute to economic growth. If discovery is to come to the aid of our great global challenges in climate change, poverty, and disease, we have no choice but to become much better at linking discovery, innovation, and entrepreneurship.

Universities and research institutions are engines of innovation because they are the major source of discovery, new technology, and scientifically trained people. Technology companies arise on the boundaries of universities for many reasons: Translation of the science is accelerated by the recruitment of recently trained personnel and by consultation with academic scientists involved in discovery and invention; the literal proximity of basic and applied scientists with entrepreneurs fosters conversations and collaborations, accelerating the translation process. This is plainly illustrated in a schematic of the area around MIT in Cambridge, Massachusetts, called the Kendall Square Cluster (Fig. 1). The buildings shown in yellow are on the MIT campus along the Charles River, and around MIT are a large number of high-tech companies. Every blue box is a biopharma company, green is energy, orange is information technology/data, and red is venture capital. Similar clusters are found around campuses in California, Ohio, and many other locations. This immediate proximity of research institutions, high-tech companies, and venture capital highlights the fact that even in this age of the Internet and rapid transport, local interactions are still vital. Leaders across the world recognize this and are establishing research institutes to stimulate local innovation.

LIFE SCIENCES REVOLUTIONS

The history of advances in life sciences at the molecular level and the resulting innovation provides an excellent illustration of discovery and innovation. This history begins in 1953, when Watson and Crick announced the structure of DNA and deduced how genetic information is transmitted when cells divide. This single event, which extended Darwin's theory of evolution and Mendel's discovery of the transmission of genes, took life sciences into a new realm. Just as Newton's principles were the first general statement of the physical mechanistic laws of nature, the discovery of the structure of DNA was the first mechanistic explanation of inheritance in terms of physical laws. The importance of this analogy is that Newton's principles appeared some 200 years before Watson and Crick. Much of the technology of our contemporary economy is built on the laws of Newton. In contrast, life science at the molecular level is very new and will take centuries to mature as an economic force in society.

After the discovery of the structure of DNA, the next 10 years of molecular biology were highlighted by the research of the great French biologists Jacob and Monod, who discovered the steps in the flow of information from DNA to proteins through the intermediate of RNA (Fig. 2). This discovery, along with the elucidation of the genetic code, established how information in DNA is transferred within the cell to synthesize cellular proteins and thus other components.

Another decade passed, during which scientists in academic institutions around the world, motivated by curiosity about the

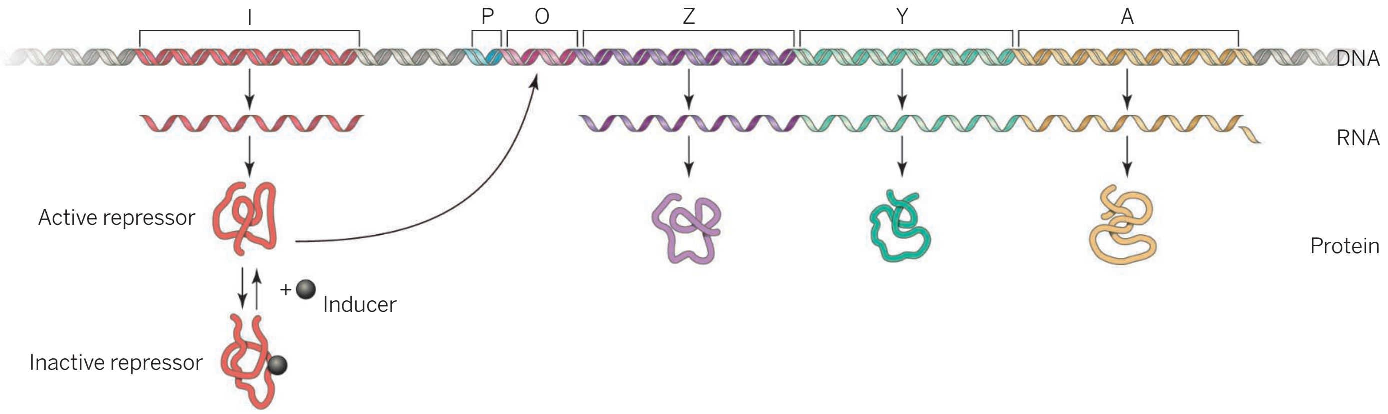

Fig. 2. The original operon model of Jacob and Monod, as proposed for the regulation of the *lac* genes of *E. coli* in 1961 [modified from (*4*)].

secrets of the gene, investigated biology at the molecular level. This produced three advances in the mid-1970s that changed society: recombinant DNA, DNA sequencing, and chemical synthesis of DNA. In theory and then practice, these discoveries empowered scientists to use all of the complexities of billions of years of evolution to innovate in the creation of new genes and organisms. In the mid-1970s, for the first time in history, life sciences became a synthetic science, much as chemistry had more than a century earlier. Biotechnology, as an innovative industry, arose at this time to translate the new science into products for meeting global needs. The first of these innovations was in health care, where replacement of animal insulin with human insulin benefited diabetics. This was followed by new vaccines, new types of treatments for previously untreatable diseases, and even control of the progression of AIDS by combinations of drugs. It was clear at the earliest stages of biotechnology that it would also contribute to providing new sustainable food sources, energy sources, and materials.

The initial appearance of biotechnology in the late 1970s and early 1980s signaled the transition from the first revolution in life sciences, the discovery of the structure of DNA, to the second revolution, the sequencing of the human genome (Fig. 3). This initiative began in the late 1980s and early 1990s and was completed in the early 2000s, with the draft sequence in 2001 and the complete sequence in 2003. There have been many innovations from the human genome initiative; for example, insights into the genetic causes of cancer and other chronic diseases. However, an often overlooked byproduct of this effort was the development of inexpensive and rapid technology to sequence DNA. With such inexpensive sequencing, we will shortly have in our computers the sequences of billions of genes from most species on our planet, from the plant, microbial, and animal kingdoms. These genes contain a record of 4 billion years of evolution from shortly after Earth's surface cooled to current times. Some of these genes allow organisms to metabolize an extensive set of compounds for energy, others render cells resistant to pathogens and toxic compounds, and others mediate communication with other organisms to live in a symbiotic relationship. When you picture this vast storehouse of diverse genes with novel functions as a resource for further synthesis of new organisms with innovative capacities, you get a glimpse of society's future.

THE NEXT REVOLUTION: CONVERGENCE

What is the next revolution in life sciences? Many think that an important part of the blueprint for future innovations is the integration, or convergence, of other disciplines with life science. I was fortunate to co-chair, with Tom Connelly of DuPont Corporation, a 2009 National Academy of Sciences report entitled *A New Biology for the 21st Century*. The report emphasized the importance of the convergence of life sciences with engineering, physical, mathematical, and computational sciences in meeting future challenges.

Susan Hockfield, MIT president emeritus, relates this revolution to a historical advance: "Physicists gave engineers the electron, and they created the IT revolution. Biologists gave engineers the gene, and together they will create the future."

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Note the two parts of this statement. First it acknowledges that recent advances in life sciences have prepared the stage for rapid innovation. In contrast to biologists leading engineers in their research and innovation with genes, biologists "gave" the "gene," thus empowering engineers in life sciences. The statement also indicates that it is important that biologists and engineers integrate, and together they will create the future. Thus, convergence encompasses engineers and physical scientists applying their knowledge and tools to problems in life science in their own professional domains. An example would be developing new statistics, thermodynamics, and chemistry to explain the origins of life, or developing new computational tools and computer cores to detect signals in vast amounts of clinical data. Convergence is also the collaboration of life scientists with engineers and physical and computational scientists. Hence, the emerging thrust of convergence recognizes the current value and future promise of expanding engagement of these diverse disciplines in life sciences to meet societal challenges.

Convergence is beginning to be recognized in the funding of new U.S. national initiatives, such as in synthetic biology, nanotechnology, and most recently in the Presidential BRAIN Initiative. However, these small but important initiatives are insufficient to capture the promise of convergence. I outline below examples of areas in which larger investment in convergence may have great impact.

Climate change and a future population of 9 billion are a volatile combination for food security. In meeting this challenge, adaptation of plants to a broader range of environments is critical to increase the amount of arable land and distribute production to locations where it is needed to reduce hunger. This should be possible with modern genetic technology and the consideration of agricultural environments as an ecosystem. Accomplishing this calls us to face the question of the adoption of GMO technology. This technology has proven itself safe and effective in increasing the productivity of agriculture over the past decades. It has now spread beyond a small number of companies and is being developed to improve the nutritional content of plants and protect against rapidly spreading pathogens destroying local crops. In a 2013 article (*6*), *Technology Review* posed the question, "Can we meet the global food challenge without widespread adoption of GMO plants?" The answer, in my opinion, is "no."

An important opportunity for meeting the energy challenge of replacing fossil hydrocarbons with a sustainable source is then expand ecosystem engineering to reduce further damage and restore ecosystem functions. Part of this promise is the application of DNA sequencing to analyze the range of microorganisms in healthy and damaged environments. These organisms are the foundation of the food chain, and shifts in their population will eventually drive change through the surrounding environment. Another part is the development of imaging and detection systems that will report in real time about changes in an ecosystem. In many cases, it will be as easy to collect a lot of information in parallel about an environment as making a measurement of a few constituents. Over time, synthesis of this information can provide profound insights that are actionable.

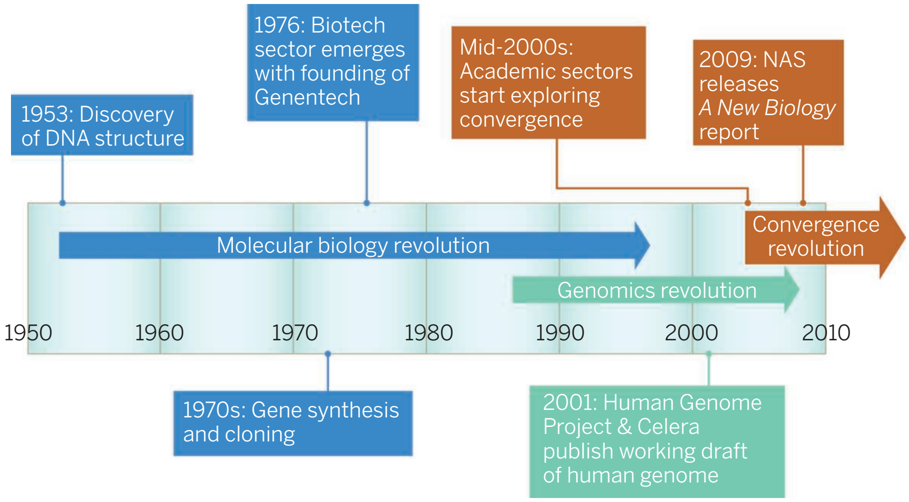

Fig. 3. Timeline: The three life sciences revolutions, leading to convergence [source (*5*)].

the production of transportation fuels from biomass. As was obvious from the beginning of discussions of alternative energy sources, corn grain, which is used in animal and human nutrition and thus expensive, cannot in the long term be the biomass used in this process. To make a real impact on the energy challenge, many integrated innovative systems need to be developed in which plants are designed specifically to be used as biomass, microorganisms are designed for conversion of this biomass to hydrocarbon-type compounds, and manufacturing processes are engineered for efficient production and distribution. The engineering of integrated synthetic biology and manufacturing processes is rapidly advancing to make this a reality. For example, bio-based polymers are beginning to replace hydrocarbon-based polymers in many consumer products (*7*).

Convergence will also help meet our environmental challenges. Convergence strategies could help us develop better monitoring for changes in ecosystems and

Increasing the quality of health care in a cost-effective fashion is dependent upon using information technology and advances in life sciences and medicine to assess, inform, and modify lifestyles and better treat individuals. The development of biotechnology is the first step along this path. Merging media, personal communication tools, and the application of medical data to the point of care of individual patients are other important advances. Innovation along these lines will require a broad convergence of social, mathematical, physical, and engineering sciences with the medical, regulatory, and financial communities. For example, if we could use modern genomic technology at the stage of diagnosis to distinguish cancers that will progress to lethality from those that are indolent, it would both improve cancer care and reduce costs.

The promise of convergence is dependent upon continued investment in basic science and translation of the resulting discoveries into innovations. This will not happen without expansion of current public/private partnerships, with the public sector funding more of the basic research and the private sector funding more of the translational activities. Increase in investment by public agencies needs to happen now. Some of this investment should focus on training the next generation of scientists and engineers. In furthering convergence, this generation of students and fellows would benefit from enhanced communication and collaboration with one another during training in multidisciplinary environments. Another issue that needs to be considered is the limited research funds for engineering and computational scientists to investigate life sciences outside of National Institutes of Health (NIH) support, as many scientists from these domains feel unappreciated by NIH's application and review processes. Government investments in research in many countries, including the United States, have fallen in purchasing power over the past decade. This will result in a slowing of growth in innovation and the economy in the future.

To meet oncoming global challenges, we will need to better link discovery, innovation, and entrepreneurship. In the past, we simply assumed that they would converge as a matter of course, but given their importance, the linkages should be considered more closely. In parallel with strengthening these linkages, we will need stronger cross-discipline integration via the convergence model, joining the life, engineering, social, and physical sciences into common pursuits. This means convergence on both fronts, across the sciences as well as between science and implementation. I end with the following question: "Can we meet future global challenges without such convergence?" I think the answer is "no."

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