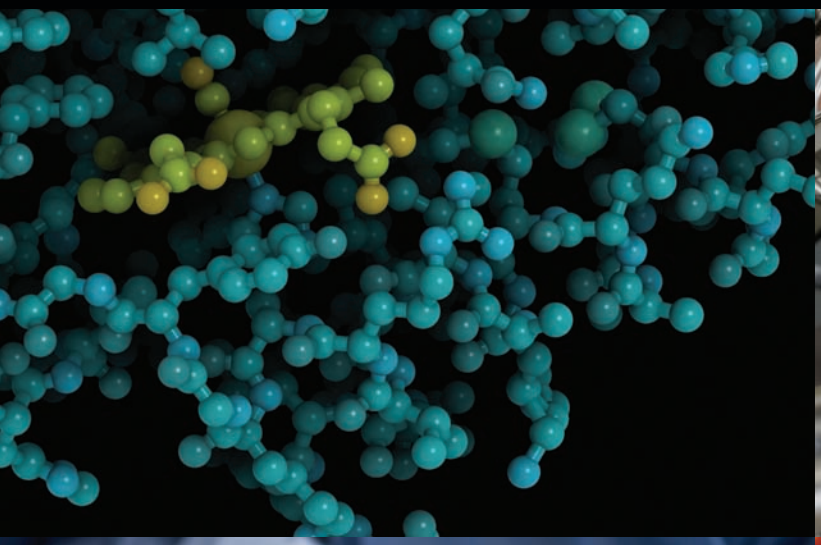
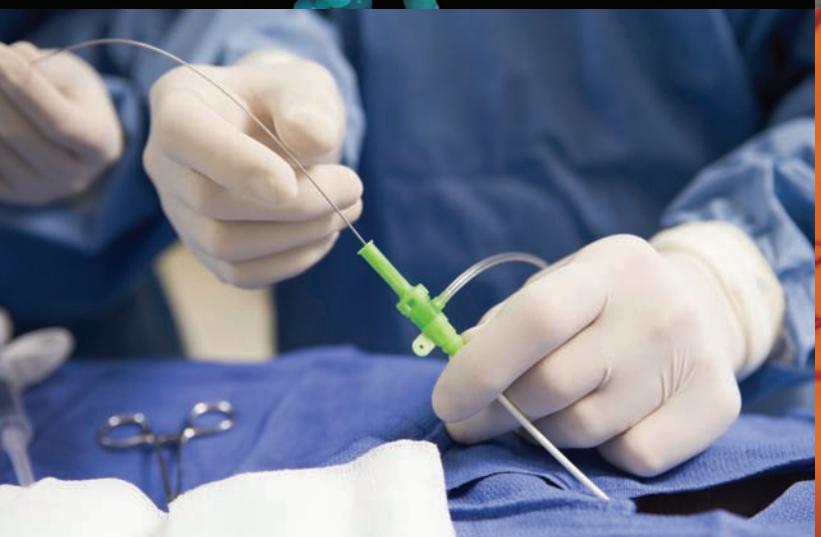
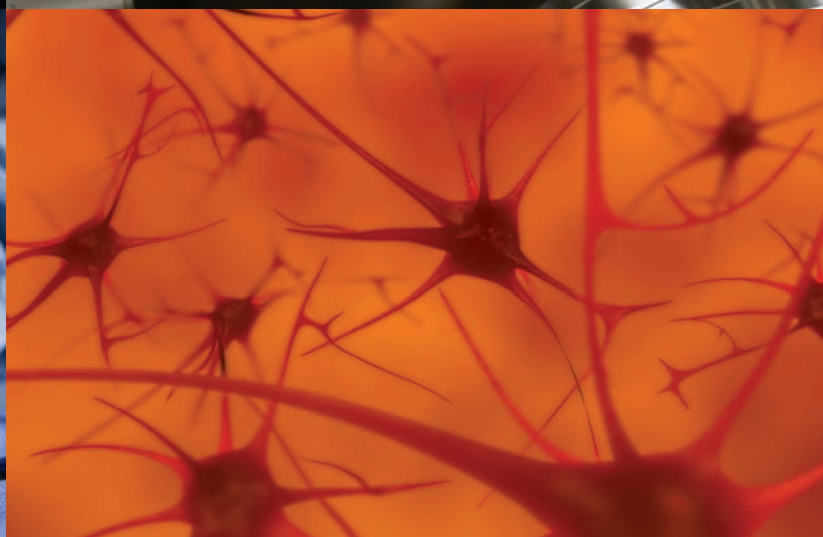
MASSACHUSETTS INSTITUTE OF TECHNOLOGY

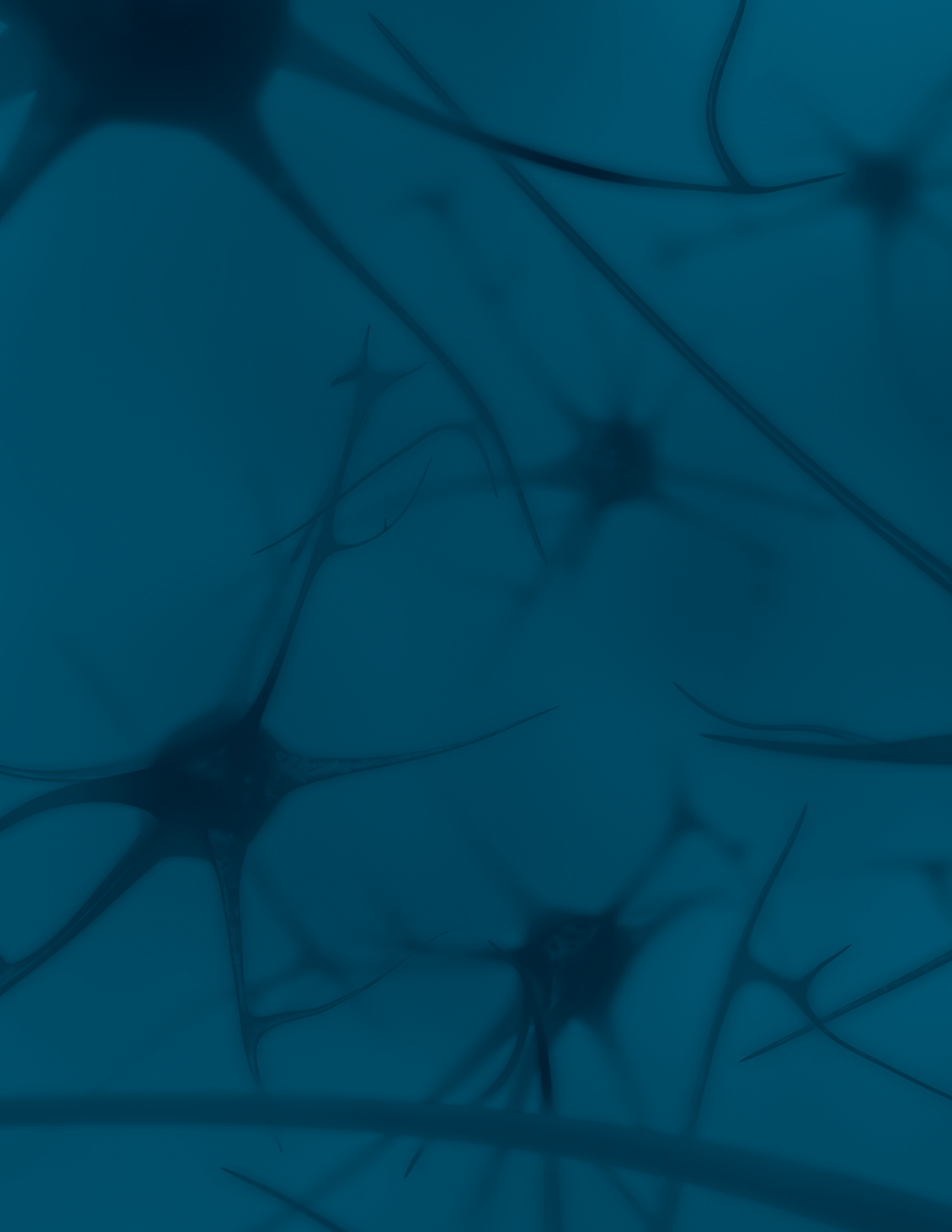
The Third Revolution:

The Convergence of the Life Sciences, Physical Sciences, and Engineering









January 2011

Letter to our Colleagues:

This report is presented to the health science research community to help delineate an important new research model—convergence—which draws on an ongoing merger of life, physical and engineering sciences.

This new model is being adopted at many institutions in different forms. The past decade has seen the evolution of new interdisciplinary research areas—bioinfomatics, synthetic biology, nanobiology, computational biology, tissue engineering, biomaterials, and systems biology are examples. These new fields share a comparable, underlying research model, convergence, and there is a need to see them as a unity in order to ensure their continued progress. The successful application of this model will require not simply collaboration between disciplines, but true disciplinary integration.

Convergence will be the emerging paradigm for how medical research will be conducted in the future. However, convergence faces a series of policy challenges that must be resolved to allow it to emerge at a scale that could be truly transformative.

The report that follows attempts to define this new research model, offers a series of cases to indicate its promise, reviews the role of the new model in improving the economics of health delivery, and offers a series of policy recommendations to better implement it. We thank staff at MIT's Washington Office for assisting in this effort, including Amanda Arnold, Alison Fox, Kari McCarron, Bill Bonvillian, and Tracy Kambara. We, as faculty at MIT, offer this report to both encourage dialogue with our colleagues at many different institutions who are likewise adopting this new model as well as introduce convergence as a blueprint for innovation to others. We look forward to your questions and ideas.

Sincerely,

Phillip A. Sharp
Institute Professor and Professor of Biology

Charles L. Cooney
Robert T. Haslam Professor of Chemical Engineering

Marc A. Kastner
Dean, School of Science, Donner Professor of Science

Jacqueline Lees
Professor of Biology and Ludwig Scholar,
Associate Director, Koch Center for Integrative Cancer Research

Ram Sasisekharan
E. H. Taplin Professor of Health Sciences and Technology,
Director, Harvard-MIT Division of Health Sciences and Technology

Michael B. Yaffe
Professor of Biology

Sangeeta N. Bhatia
John and Dorothy Wilson Professor, Harvard-MIT Division of Health Sciences and Technology

Tyler E. Jacks
David H Koch Professor,
Director, Koch Institute for Integrative Cancer Research

Douglas A. Lauffenburger
Ford Professor and Head, Department of Biological Engineering

Robert Langer
David H. Koch Institute Professor

Paula T. Hammond
Bayer Professor of Chemical Engineering

Mriganka Sur
Paul E. Newton Professor of Neuroscience, Head,
Department of Brain and Cognitive Sciences

Convergence is a new paradigm that can yield critical advances in a broad array of sectors, from health care to energy, food, climate, and water.

For more information about this report,

contact the MIT Washington Office:

820 1st St. NE, Ste. 610

Washington, DC 20002

202.789.1828 || 617.324.9981

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The Convergence of the Life Sciences Physical Sciences and Engineering

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Introduction

There are few challenges more daunting than the future of health care in this country. This paper introduces the dynamic and emerging field of convergence—which brings together engineering and the physical and life sciences—and explains how convergence provides a blueprint for addressing the health care challenges of the 21st century by providing a new knowledge base, as well as a new generation of diagnostics and therapeutics. We discuss how convergence enables the innovation necessary to meet the growing demand for accessible, personalized, affordable health care. We also discuss the role of government agencies in addressing this challenge and providing funding for innovative research. Finally, we recommend strategies for embedding convergence within agencies like the National Institutes of Health (NIH), which aims to optimize basic research, improve health technology, and foster important medical advances.

1. Overview of Convergence

What exactly is convergence? We define it as the merging of distinct technologies, processing disciplines, or devices into a unified whole that creates a host of new pathways and opportunities. It involves the coming together of different fields of study—particularly engineering, physical sciences, and life sciences—through collaboration among research groups and the integration of approaches that were originally viewed as distinct and potentially contradictory.

We see convergence as a blueprint for innovation. Advances in information technology, materials, imaging, nanotechnology, optics, and quantum physics, coupled with advances in computing, modeling, and simulation, have already transformed physical science. They are now beginning to transform life science as well. Convergence takes the technical tools, as well as the "disciplined design approach" traditional to engineering and physics, and applies them to life science research. But convergence is not a one-way street; biological models are simultaneously transforming engineering and physical science. Advances in biofuels, biomaterials, and viral self-assembly are just a few examples of this reciprocal relationship.

"We see convergence as a blueprint for innovation."

The convergence revolution is a paradigm shift, but not just, in Thomas Kuhn's terms, a paradigm shift *within* a discipline.[1] Convergence means a broad rethinking of how all scientific research can be conducted, so that we capitalize on *a range* of knowledge bases, from microbiology to computer science to engineering design. In other words, the convergence revolution does not rest on a particular scientific advance but on a new integrated approach for achieving advances.

A major beneficiary of convergence will be biomedicine, as interdisciplinary research enhances our existing knowledge and leads to new medical treatments. From the infusion of different ideas and background designs, researchers are already making exciting discoveries—new drug delivery mechanisms at the nanoscale, improved chemical and disease sensing, new predictive computer models of disease, new capabilities to modify genetic disorders, and cost-effective biometric analysis for personalized medicine. By recognizing convergence as a transformative trend, we hope to offer a new vision for the future and build

[1] Thomas S. Kuhn, *The Structure of Scientific Revolutions,* 3rd ed. (Chicago: University of Chicago Press, 1996).

awareness of new opportunities for the United States to continue leading the world in biomedical innovation.

Thought leaders at the National Academies of Sciences and elsewhere in the administration are convening study panels and workshops to discuss the intersection of scientific disciplines,[2] but more must be done. Because of its cross-disciplinary nature, convergence challenges the historic structure of universities, which are organized into departments focusing on discrete disciplines. Furthermore, convergence-style research does not fit neatly within the funding categories of the federal research-support agencies, nor does it align neatly with the missions of these research institutes. It is imperative that we continue efforts to overcome this problem of "stovepipes" and develop both new investment mechanisms and new models for organizational collaboration.

Already, the push to work across disciplines is escalating within the research community and coming to the attention of science policy makers, who are moving the conversation beyond the integration of disciplines and calling for convergence to be embedded into America's R&D system. For instance, in his remarks at the annual meeting of the National Academy of Sciences in 2009, President Obama referred to the vast potential that a cross-cutting federal initiative on convergence could have for biomedical research:

> In biomedicine, we can harness the historic convergence between life sciences and physical sciences that's underway today; undertaking public projects—in the spirit of the Human Genome Project—to create data and capabilities that fuel discoveries in tens of thousands of laboratories; and identifying and overcoming scientific and bureaucratic barriers to rapidly translating scientific breakthroughs into diagnostics and therapeutics that serve patients.[3]

Similarly, two members of the President's Council of Advisors on Science and Technology wrote in 2010 about the merging of information technology, biotechnology, and nanotechnology:

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[2] See National Research Council Committee on Biomolecular Materials and Processes, *Inspired by Biology: From Molecules to Materials to Machines* (Washington, DC: National Academies Press, 2008); National Research Council Committee on Forefronts of Science at the Interface of Physical and Life Sciences, *Research at the Intersection of the Physical and Life Sciences* (Washington, DC: National Academies Press); and National Research Council Committee on a New Biology for the 21st Century, *The Role of Life Sciences in Transforming America's Future: Summary of a Workshop* (Washington, DC: National Academies Press, 2009), http://books.nap.edu/openbook.php?record_id=12592.

[3] Barack Obama, "Remarks by the President at the National Academy of Sciences Annual Meeting," Washington, DC, April 27, 2009, http://www.whitehouse.gov/the_press_office/Remarks-by-the-President-at-the-National-Academy-of-Sciences-Annual-Meeting/.

> Each of these research fields has the potential to enable a wealth of innovative advances in medicine, energy production, national security, agriculture, aerospace, manufacturing, and sustainable environments—advances that can in turn help create jobs, increase the nation's gross domestic product (GDP), and enhance quality of life. In combination, through what some have called the nano-bio-info convergence, the potential for these fields to transform society is even greater.[4]

The impact of convergence will not be limited to medicine; other scientific areas stand to benefit as well. An important report by the National Academy of Sciences suggests that convergence can yield critical advances in a broad array of sectors, including energy, food, climate, and water.[5] In this white paper, however, we focus on the application of convergence in health research because we believe that this field is ripe for new discoveries and can powerfully demonstrate the benefits of convergence.

Recent Biomedical Revolutions

There have been two dramatic developments in life science research in the last 50 years—the molecular and cellular biology revolution and the genomics revolution. These two revolutions paved the way for the convergence revolution now taking shape. We believe that combining knowledge of engineering and physical science with life science expertise will build on recent advances in molecular and cellular biology and genomics and produce new breakthroughs. Of course, we are not suggesting that we have reached the pinnacle of research in molecular and cellular biology or genomics; there is still much more to be discovered. However, convergence offers an exciting opportunity to enrich present and future research in these fields—and in others.

The First Revolution: Molecular and Cellular Biology

The first biological-science revolution involved the use of molecular and cellular biology to understand cells and diseases. This revolution began with the discovery of the structure of DNA by James D. Watson and Francis Crick in 1953 and the birth of molecular biology. In the early 1970s, this led to the development of genetic engineering—combining DNA from different organisms to produce new products and processes. Leaders in the field, like Salvador Luria, quickly built on this game-

[4] Shirley Ann Jackson and Eric Schmidt, "Polishing Technology's Golden Triangle," Office of Science and Technology Policy blog, June 15, 2010, http://www.whitehouse.gov/blog/2010/06/15/polishing-technology-s-golden-triangle.

[5] National Research Council of the National Academies. *A New Biology for the 21st Century* (Washington, DC: National Academies Press, 2009), http://www.nap.edu/openbook.php?record_id=12764. For a related video, see http://www.youtube.com/watch?v=BOJHhAMFDOw.

changing discovery and started disease-specific research centers at universities to apply the new understanding of the structure of viruses and cancerous cells.

Researchers concluded that they could truly understand disease only if they understood it at the molecular level inside the cell. The new field of molecular and cell biology allowed researchers to probe the inner workings of diseased cells. By doing so, they made remarkable advances in understanding cancer and other diseases. Funding and other support came from the government; in 1974 the NIH's National Cancer Institute (NCI) set up basic science centers for cancer research (CCRs) where experts in molecular biology, immunology, cell biology, virology, human genetics, and chemical carcinogenesis could collaborate with cancer biologists, clinical oncologists, prevention experts, and surgeons. In creating the CCRs, NCI recognized that new scientific advances require innovative institutional support mechanisms.

"Researchers concluded that they could truly understand disease only if they understood it at the molecular level inside the cell."

Soon enough, entrepreneurs launched the biotechnology industry by founding companies such as Genentech, Biogen, and Amgen, where university-trained researchers could translate the new technology into products. The biotech industry has generated treatments for some of the most dreadful human diseases, such as cancer, multiple sclerosis, and hepatitis, and created tens of thousands of jobs.

The Second Revolution: Genomics

The second major revolution in life science research in recent decades is the genomic revolution. It encompasses a drive to study an organism's entire genome—reading the basic DNA sequence, identifying the physical location of discrete genes, and understanding intragenomic phenomena. This revolution got off the ground when the Department of Energy began funding projects to apply supercomputing to genetics research. As time went on, genome research shifted to NIH.

NIH progress on sequencing the human genome began with genetic and physical mapping and systematic DNA sequencing. Progress accelerated greatly when researchers introduced faster instrumentation and computer techniques that allowed sequencing of the genome in a much shorter time frame. This in turn sparked one of the most creative competitions in science history, as NIH's Human Genome Project, led by Francis Collins (President Obama's later choice for NIH director), and Celera's team, led by Craig Venter, vied to adapt the new technology and combine it with previous mapping results. The two teams eventually announced success jointly, with parallel human genome maps printed on the same day in *Nature* and *Science* magazines, providing an enormously useful new tool set for understanding the basis of human disease.

The achievements in genome mapping also heralded a new era in biomedical research. If the molecular biology revolution enabled diseases to be understood at the molecular, "hardware" level inside the cell, the genomics revolution enabled an understanding of the "software" that drives cell processes.

The advances in genomic science have made it possible to identify the genetic foundations of many diseases, which is the first step in developing new treatments. Genetic mapping is also critical to developing personalized medicine—treating patients with preventive and curative therapies tailored to their unique genetic makeup and shown to be effective for their specific disease subtype, thereby avoiding costly, ineffective medication and harmful side effects.

The Third Revolution — Convergence

Much of the exciting scientific research now occurring involves combining molecular and cellular biology with genomics, engineering, and knowledge of the physical sciences. As we are beginning to see, convergence thus constitutes a third great revolution in life sciences and biomedical research.

This illustration helps to view these three revolutions over time.

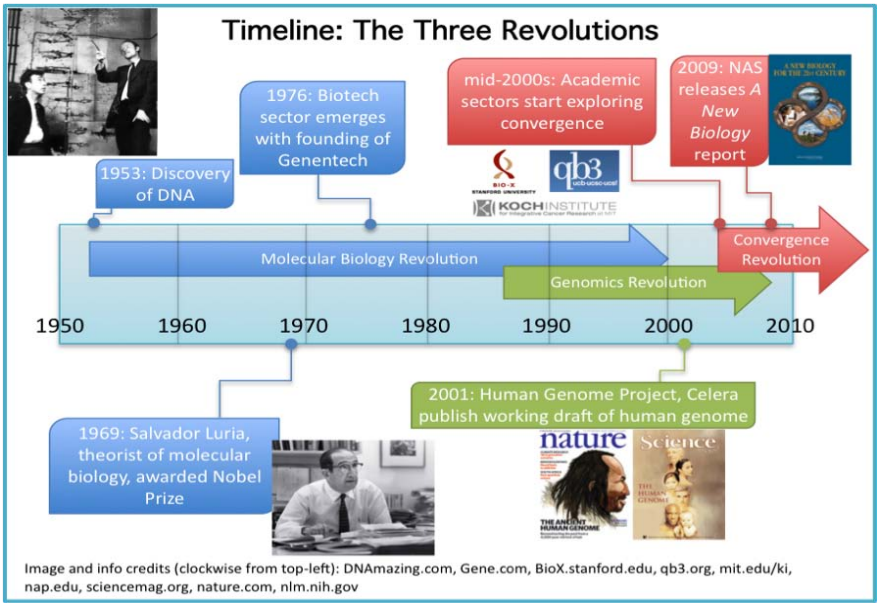

Figure 1: Timeline highlighting some events related to the molecular biology, genomics, and convergence revolutions.

As already noted, convergence does not simply involve a transfer of tool sets from one science to another; fundamentally different conceptual approaches from physical science and engineering are imported into biological research, while life science's understanding of complex evolutionary systems is reciprocally influencing

physical science and engineering. Convergence is the result of true intellectual cross-pollination.

A number of university-housed centers have already emerged as showcases of convergence, providing the intellectual and research space for life scientists to interact and collaborate with physical scientists and engineers. NIH has been critical to this effort, especially in cancer research. For example, the National Cancer Institute (NCI) created eight Centers of Cancer Nanotechnology Excellence for interdisciplinary and cross-university projects. These centers are pursuing a variety of activities, including developing nanoscale devices for targeted drug delivery, for diagnostics, for noninvasive imaging, and for molecular sensing of cancers, with an emphasis on prostate, brain, lung, ovarian, and colon cancers.

NCI also created nine Integrative Cancer Biology Program Centers throughout the country that exemplify convergence. These centers are pursuing a systems-biology approach to ascertain what the most effective cell regulatory nodes might be for understanding and treating cancer. This work has direct application to identifying the best diagnostic and delivery targets for the new nanotechnology tools.

"Convergence is the result of true intellectual cross-pollination."

Of course, applying engineering to health is not a novel idea. The birth of the X-ray in 1895, for example, gave way to a revolution in imaging that led to the electrocardiograph in the early 1900s, followed by computerized axial tomography (commonly know as the CAT scan) in the 1970s, and the first commercial MRI (magnetic resonance imaging) scanner in the 1980s. These inventions required the merging of multiple disciplines. However, a concentrated focus on convergence can spur even more innovation. Viable commercial products have already developed from this approach. The advanced DNA sequencers are excellent examples. The new Illumina genome sequencer, for instance, is helping to lower the cost of a full genome sequencing from billions of dollars (the price tag when the first genome was mapped) to under $10,000.[6] More convergence-style research is already under way.

Examples of Convergence in Biomedical Research

Convergence breakthroughs depend not only on new research institutions where different disciplines can find common space, but also on collaborative, interdisciplinary research teams that operate within them. The work of some leading biomedical research teams is summarized below to provide concrete illustrations of convergence in action. Several of the convergence examples are

[6] "New Illumina Genome Sequencer Dramatically Slashes Costs, Time," online article at Seeking Alpha, Jan. 16, 2010, http://seekingalpha.com/article/182969.

drawn from MIT because we are most familiar with them, but comparable research is starting to evolve at many research centers.

Computational Biology for Immune Response

Background: Advances in computational simulation and modeling analysis achieved through supercomputing opened the door to the genomics revolution. The developing field of computational biology combines computer science, physics, and engineering with molecular and genetic biology to elucidate mechanistic principles that could lead to the rapid identification of candidate gene and cellular targets for new therapies.

For example, researchers in Arup Chakraborty's lab at MIT have used theoretical and computational approaches to uncover new mechanistic principles underlying the adaptive immune response to pathogens.[7] By bringing statistical mechanics together with engineering analyses of chemical kinetics and genetic, biochemical, and imaging experiments, as well as clinical data, Chakraborty's team has described the molecular mechanisms underlying how T lymphocytes (essential for adaptive immunity) develop, detect, and recognize the molecular signatures of pathogens displayed on the surface of other cells. This research is revealing new principles that govern the immune response to HIV and the emergence of T lymphocyte-mediated autoimmune diseases.

Significance: In using advanced computational models to apply statistical mechanical methods to highly complex biological systems, Chakraborty's convergence approach has led to new understanding of how the body's immune response operates. This new knowledge has, in turn, created the opportunity to better manage the immune response against disease. For example, there is usually an inadequate immune response to HIV infections, and multiple sclerosis results from an inappropriate immune response against the body's own nervous system. Gaining a complete understanding of how T lymphocytes work in adaptive immunity may provide additional avenues for the development of therapies and potential cures. This groundbreaking theoretical work has had a major impact on experimental cellular and molecular immunology as well.

Imaging Technology to Prevent Blindness

Background: Advances in biomedical imaging have already led to breakthroughs in the way diseases are diagnosed and treated. MRIs and other scans are now widely used to detect various disorders as well as common bone injuries, and they provide doctors with powerful new tools in the battle against eye disease.

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[7] Arup Chakraborty is a professor of chemical engineering, chemistry, and biological engineering at MIT. For details about his lab, see http://web.mit.edu/akcgroup/.

Because testing the eye's retina by removing tissue causes damage to the retina, laser imaging has been evolving as an alternative way to diagnose diseases that cause blindness. However, patients can keep their eyes still for less than a second—not enough time for existing lasers to measure early onset of disease. In the 1990s, researchers developed optical coherence tomography (OCT), a new way to scan lasers back and forth at high speeds. In 2007, James Fujimoto's research group at MIT created new OCT scanning technology that could record 236,000 lines per second, a speed 10 times faster than was previously possible.[8] This new method combines two-dimensional cross-sectional images of the retina to form a highly precise three-dimensional picture of the eye. This technology may become a critical new diagnostic tool for eye diseases, as important as ultrasound is for other fields.

Significance: The aging population of the U.S. is increasingly afflicted with disabling eye diseases. The new OCT-based imaging technology made possible by the convergence of physics, optics, electrical engineering, and physiology will enable doctors to spot even the most subtle changes resulting from diseases of the retina, such as diabetic retinopathy, glaucoma, and age-related macular degeneration, which are collectively the leading causes of blindness. This new technology could also rapidly increase the speed with which doctors can take detailed images of the eye to diagnose and treat problems. Early treatment will improve the quality of life for hundreds of thousands of Americans and will lower medical costs by addressing issues before they become more serious.

Nanotechnology for Targeted Chemotherapy Delivery

Background: Researchers have begun to use nanoparticles to transport time-release anticancer drugs directly to cancerous cells, such as those in the prostate. Nanoparticles, each a tiny fraction of the size of a human cell and engineered to be accepted by certain cells within the body, can deliver strong doses of therapeutics to a specific location. A team of MIT researchers under Francesco Stellacci and Darrell Irvine has demonstrated the engineering of nanoparticles into homing devices or "smart bombs" that improve drug delivery by targeting only cancerous cells.[9]

There are several significant challenges with this drug delivery system. First, researchers must isolate homing devices, such as RNA molecules called aptamers that bind specifically to tumor

"A team … has demonstrated the engineering of nanoparticles into homing devices or 'smart bombs' that improve drug delivery by targeting only cancerous cells."

[8] James Fujimoto holds appointments in MIT's Electrical Engineering and Computer Science Department and in the Research Laboratory of Electronics. For details about his research, see http://www.rle.mit.edu/lmmi/index.htm and http://www.rle.mit.edu/OQE/.

[9] Francesco Stellacci and Darrell Irvine are members of the faculty in MIT's Department of Materials Science and Engineering.

antigens and will be taken up by cancer cells. Another challenge is constructing a safe, biodegradable nanoparticle that can carry a drug on the inside and bind to an aptamer on the outside. A further difficulty has been developing a synthetic material that can pass through a cell membrane without destroying the cell. Stellacci and Irvine's research at the convergence of engineering and biology demonstrated that gold nanoparticles coated with alternating bands of neutral and negatively charged molecules, known as "striped" nanoparticles, can quickly penetrate the protective cell membrane without killing the cell.

Significance: A major problem with current chemotherapy drugs is that they do not effectively discriminate which cells they kill, causing toxic side effects such as nausea, hair loss, and, more significantly, weakened immune systems. By targeting drug delivery to cancerous cells through nanoparticles, it may be possible to avoid the harmful effects of chemotherapy. However, only through the convergence of materials science, engineering, chemistry, and biology can a nanoscale drug delivery device be successfully developed further for clinical use.

Brain Grafts for Treating Brain Disorders and Injury

Background: The convergence revolution is creating major new opportunities in neuroscience, a field within the life sciences that has traditionally attracted researchers from divergent backgrounds such as electrical and computer engineering and chemistry. We are learning that the adult brain constantly adapts to changes in stimuli; this plasticity appears not only as learning and memory, but also as dynamic changes in information transmission and processing. Researchers are working to understand long-term brain plasticity and short-term dynamics in networks of the developing and adult cortex to understand the mechanisms underlying many of the neurological diseases and conditions that challenge the nation's health care providers.

Researchers such as MIT's Mriganka Sur[10] are using state-of-the-art techniques developed from physical and engineering sciences, including:

- two-photon and confocal microscopy of cells, synapses, and molecules in vitro and in vivo
- multiple-electrode, single-unit recording in the cortex
- high-resolution optical imaging of activity from an expanse of cortex
- whole-cell intracellular recording in slices and in the intact brain
- microarrays and computational tools to identify genes in specific tissues.

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[10] Mriganka Sur is a professor of neuroscience at MIT and head of the Department of Brain and Cognitive Sciences. For details about his lab, see http://web.mit.edu/picower/faculty/sur.html.

Significance: Recent neuroscience research using technologies adapted from other fields has shed light on the true nature of the adult brain. By "rewiring" the developing brain, and by revealing remarkably widespread changes in the adult cortex during learning, research is demonstrating that the brain is far more plastic and adaptable than was previously believed. With this additional information, researchers are pursuing innovative responses to neurological disease and injury, including the development of networks of neurons grown in vitro that could one day serve as "brain grafts" to treat victims of traumatic brain injury or stroke.

Bacterial Plasticity for Tumor Detection and Drug Delivery

Background: A major challenge for medical researchers has been developing drugs that effectively fight diseases but do not damage healthy tissues and cells in patients. Scientists have attempted to solve this problem from a biological perspective by focusing on cell markers and immunological concepts. Although this approach has had some success, convergence-driven methods to optimize drug delivery are gaining momentum.

Chris Voigt's lab at the University of California, San Francisco, specializes in reprogramming bacteria to perform functions useful for biomedical and industrial applications.[11] The Voigt lab created E. coli bacteria that carry density sensors taken from another bacterial species. When the E. coli are introduced to mammalian cells, the density sensors can detect how densely packed the mammalian cells are, based on environmental cues such as oxygen levels. In addition, above a certain density, the sensors trigger the E. coli to invade the mammalian cells by activating an enzyme called invasin. This bioengineering feat shows promise for drug delivery, especially against cancers. Cancerous cells tend to form tumors, which are high-density clusters of cells that can be detected by the bacterial sensors. If the E. coli can be further engineered to carry anticancer drugs, this system can be used for targeted therapy. Because the cancer cells are clustered together, they would be detected by the bacteria and the drug would enter and kill those cells, leaving healthy cells unharmed.

Significance: Voigt's bacterial creation is a prime example of convergence in which engineering principles are applied to a biological system. The lab essentially copied the sensor gene in one bacterial species and inserted it in another. This experiment's potential for drug delivery would require even more collaboration across the disciplines; for example, chemistry would be required to calculate the correct dosage of drugs per bacterium. Bioinformatics may help identify better bacterial species, sensor genes, or anticancer drugs for human therapeutic use, as more information becomes available. Ultimately, this bacterial-sensor drug delivery system would reduce the side effects of chemotherapy and other risky treatments

[11] Chris Voigt is an associate professor in the Department of Pharmaceutical Chemistry at The University of California, San Francisco. For details about his lab, see http://voigtlab.ucsf.edu.

that jeopardize patients' overall health while attacking the cancer. The potential medical benefits of this research demonstrate the rising need to make convergence a priority in the future of biology.

siRNA for the HIV Vaccine

Background: Interfering RNA (RNAi) is a natural process used by organisms to turn off or silence the expression of certain genes when they are no longer needed. Researchers have altered this natural process so that short interfering RNA (siRNA) can be delivered to the inside of cells to silence the genes associated with the perpetuation of diseases. The ability to silence genes in mammalian cells through RNAi has dramatically expanded the possibilities for genotype/phenotype analysis in cell biology. siRNAs have overlapping functions with microRNAs, genes normally found in mammalian cells that, when paired by partial complementarity to an mRNA, prevent production of the encoded protein. siRNA takes advantage of the existing cellular microRNA machinery to silence specific genes. Researchers have begun engineering siRNAs complementary to known disease genes, shutting off those genes and thereby providing a new type of treatment.

Significance: Although it is potentially a very powerful therapeutic tool, siRNA is difficult to dispatch across membranes to target cells. The delivery of tiny strands of RNA into target cells through nanotechnology advances gives scientists the power to knock out individual genes related to a wide variety of diseases. Now a vital tool for genomic exploration, RNAi also promises to create new drugs that would target the genetic roots of disease. For example, researchers in Phillip Sharp's lab at MIT have used siRNAs to silence genes associated with HIV entry and replication in human cells, essentially stopping the spread of the virus.[12] Similar approaches could be used to combat other diseases with a genetic mechanism. siRNA, coupled with nanotechnology advances from the physical and engineering sciences, promises a common-pathway approach cutting across disease types.

CTC-chip for Detecting Cancer Metastases

Background: Defeating cancer has been a goal of medical researchers for decades, and it is becoming clear that convergence will be required for the development of successful treatment options and detection techniques. By using physics, engineering, biology, and medicine together in the fight against cancer, doctors will be able to provide more-comprehensive treatments that approach cancer from a mechanical as well as a biological view. Such integrated research provides perhaps the best hope for attacking this life-threatening disease and lowering the cost of treatment.

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[12] Phillip Sharp is a Nobel Prize winner and Institute Professor at MIT. For details about his lab, see http://web.mit.edu/sharplab/.

Mehmet Toner directs a Boston-area research program that focuses on developing technologies for sorting and analyzing blood cells.[13] Recently, Toner's group developed the CTC-chip, a small device that shows promise for vastly improving the detection of cancer progression. Circulating tumor cells (CTCs) in the bloodstream are thought to be the root of incurable metastatic cancers, so the sooner they are detected, the sooner life-saving treatment can be started. However, CTCs are extremely rare and difficult to capture; some experts estimate the presence of CTCs to be as rare as one cell in a billion normal blood cells.

Toner's interdisciplinary work significantly improves the efficiency with which CTCs can be detected. The CTC-chip is a small chip covered with 78,000 microposts within a surface area of 970 square millimeters, and each micropost is coated with antibodies that bind to specific markers that are found on CTCs and indicate epithelial carcinomas, such as lung, colorectal, breast, head, and neck cancers. The device also contains a pump that passes the blood sample through the chip at the precise speed and angle needed to separate the CTCs from other blood cells without shearing or damaging them. As a result of the detailed physics, engineering, and biological principles that went into the development of the CTC-chip, the device is extraordinarily sensitive; in one study, the chip correctly detected CTCs in over 99 percent of cancer patients with metastases. The chip is now in clinical trials.

Significance: The CTC-chip is a shining example of convergence; it developed from the collaboration of physicists who calculated the optimal flow of blood through the chip, engineers who constructed the microposts on it, biologists who attached the appropriate antibodies onto the microposts, and clinicians who tested the chip under real-world conditions. The result is a product that could significantly alter the ability of doctors to treat cancers effectively. Doctors using the chip will be able to determine if the drugs being administered to patients are reducing their CTC numbers, and if not, then patients could quickly begin different treatments and improve their chances of survival. At the least, the CTC-chip's fine-detecting capabilities will reduce the need for repeated biopsies or expensive imaging studies on cancer patients.

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Convergent technologies promise to continue extending research frontiers and pushing medicine toward a more personalized approach that no longer accepts harmful side effects as a tradeoff for effective treatment. We argue that the groundswell convergence movement already under way should be supported by the federal government, not only because knowledge for the sake of knowledge is worth pursuing, but also because the government has a vested interest in the health of Americans and the wealth of the American economy. Investing in convergence can

[13] Mehmet Toner is a professor of surgery at Massachusetts General Hospital and Harvard Medical School, and director of the BioMEMS Resource Center (http://www.biomemsrc.org/).

solve health challenges that will overwhelm our economy under the status quo; equally important, such investment can give the United States a global competitive edge in technology development.

2. The Economic Case for Supporting Convergence

Economist and Nobel laureate Robert Solow was among the first to clearly demonstrate the relationship between innovation and economic growth. He showed that a large portion of U.S. economic growth in the early 20th century was derived from technological and related innovation.

In his work during the 1950s, Solow found that between 1909 and 1949, gains from labor and capital intensity explained only a small portion of growth in U.S. gross national product (GNP), while almost 2/3 of the remainder of GNP growth was the result of what he called "technical change."[14] His point was that technological and related innovation was the predominant causative factor behind the bulk of U.S. economic growth.

We are only now beginning to grasp the profound implications of Solow's work. In the post–World War II era, the U.S. adopted a model, currently being copied worldwide, of innovation-led comparative advantage and corresponding growth. Keeping the U.S. at the forefront of innovation is crucial to our country's economic well-being. The information technology revolution, which brought huge economic gains to the U.S. economy, especially from 1993 to 2001, is maturing, and the initial phase of the biotech revolution is playing out. Many are pondering the next phase of innovation.

There are likely to be highly fruitful economic implications, pursuant to Solow's model, for expanding U.S.-led support for the convergence of the life sciences, physical sciences, and engineering through what some are calling the "biology economy". Bringing on a new phase of technological advances that could contribute to another U.S.-led wave of worldwide innovation could be one of the keys to our future economic growth. The country is grappling with how to create a new and stronger foundation for growth; a central part of the answer is capitalizing on convergence.

Demographic Challenges and the Need for Innovation

The need to invest in biomedical research is heightened by the current health care crisis and coming demographic challenges. According to the Agency for Healthcare Research and Quality, the U.S. spends a larger portion of its gross domestic product

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[14] Robert M. Solow, *Growth Theory: An Exposition*, 2nd ed. (New York: Oxford University Press, 2000): ix–xxvi. See also Robert M. Solow, "Growth Theory and After," lecture at Nobel Prize awards ceremony, Stockholm, Dec. 8, 1987, http://nobelprize.org/nobel_prizes/economics/laureates/1987/solow-lecture.html.

(GDP) on health care than any other major industrialized country. In fact, in 2002, health care expenditures represented one-seventh of the nation's GDP and made up one of the fastest-growing components of the federal budget.[15] In addition, according to the Centers for Medicare and Medicaid Services (CMS), in 2008, total health expenditure equaled $7,681 per person.[16]

This cost issue isn't just affecting individuals and families. CMS calculated that in 2004, every state except Delaware and Wyoming spent 10 percent or more of its gross state product on health care. These statistics continue to climb, with national health expenditures expected to increase an average of 6.1 percent per year though 2019.[17]

As biomedical advances prolong American lives and as the baby-boom generation ages, our health care system will face substantial challenges, such as the inevitable rise of certain diseases and an increased need for end-of-life care. Just as cancer recently replaced heart disease as the leading U.S. cause of death (thanks to major advances in heart-disease treatment), some expect brain diseases to, in turn, displace cancer in upcoming years. Alzheimer's disease, for example, will affect the baby boomers at such an alarming rate that it is unclear how our current health care system will cope. According to the Alzheimer's Association, "the number of people aged 65 and older with Alzheimer's disease is estimated to reach 7.7 million in 2030—more than a 50 percent increase from the 5.1 million aged 65 and older currently affected."[18]

The demographic shift that the country faces becomes significantly more manageable if the baby-boom generation can remain a productive part of the workforce. This will allow their health care costs to be spread more evenly over an extended period and across the population base. Convergence, and the corresponding transformation of health care it can trigger, is key to buying us the time we will need to innovate our way through this dramatic population challenge.

Congress tried to tackle many of our health care challenges by passing the Patient Protection and Affordable Care Act (PPACA) in March 2010. PPACA attempts to ensure increased access to health care, but it is unclear how the associated costs will be managed. Cost control is critical, and it will depend to a large degree on

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[15] "Health Care Costs: Fact Sheet," Agency for Healthcare Research and Quality, Rockville, MD, Sept. 2002, p. 1, http://www.ahrq.gov/news/costsfact.pdf.

[16] "National Health Expenditure Data: NHE Fact Sheet," Centers for Medicare and Medicaid Services, Baltimore, https://www.cms.gov/NationalHealthExpendData/25_NHE_Fact_Sheet.asp (accessed July 24, 2010).

[17] Ibid.

[18] "2010 Alzheimer's Disease Facts and Figures," *Alzheimer's & Dementia* 6 (2010): 14, http://www.alz.org/documents_custom/report_alzfactsfigures2010.pdf.

innovation. New technologies and creative approaches are needed to drive productivity gains so that we can expand access to health care while also attempting to decrease the cost per person. Unfortunately, PPACA did little to address the importance of innovation. As one commentator put it, "The healthcare legislation … does not have an innovation focus … [W]e should do everything we can to encourage the sort of disruptive innovation in the medical field that has characterized the technology industry."[19]

"Cost control is critical, and it will depend to a large degree on innovation."

The demographic challenges will be upon us soon, regardless of our nation's research priorities. We will be faced with an aging population requiring greater medical attention and suffering at an alarming rate from conditions for which we still have no cures. Now is the time to prepare our medical researchers and innovators for this societal challenge by embracing convergence and all its potential benefits.

High Returns for Federal Investment in Biomedical Research

Federal investment in convergence will not only help us confront the upcoming demographic challenges in health care, it will also help us build economic wealth. Economist David Bloom points out that when we weigh decisions about whether to invest in new health technology research, we routinely undervalue the benefits of such research. This is because traditional cost-benefit analyses fail to consider that treatments and products that increase the overall health of the American people have ripple effects for the economy. Longer life expectancy and better quality of life encourage more men and women to remain in the workforce and continue to invigorate the economy.

Consider that Americans born at the end of the 20th century can expect to live about 30 years longer than if they had been born in 1900,[20] and most retirees in their 60s

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[19] Gary Shapiro, "Where Is Innovation in the Healthcare Debate?" *The Hill,* Jan. 7, 2010, p. 2, http://thehill.com/opinion/op-ed/74715-where-is-innovation-in-the-health-care-debate-. For more commentary on the need for innovation in health care, see John C. Lechleiter, "Health-Care Reform and the 'Innovation Test,'" *Wall Street Journal,* May 14, 2009, http://online.wsj.com/article/SB124227053842018311.html; and Bruce Nussbaum, "Health Care Reform Passes—Now Let's Start Health Care Innovation," *Bloomberg Business Week,* March 22, 2010, http://www.businessweek.com.

[20] Kevin Murphy and Robert Topel, "The Value of Health and Longevity," *Journal of Political Economy* 114, no. 5 (Oct. 2006): 871–904, http://www.journals.uchicago.edu/doi/full/10.1086/508033.

and 70s are physically able to work.[21] Bloom and his colleagues have calculated that a one-year increase in life expectancy improves labor productivity by a dramatic 4 percent.[22] This translates to significant economic benefit. Between 1970 and 2000, gains in life expectancy accounted for $3.2 trillion per year of national wealth, and a 1 percent reduction in cancer mortality rates was estimated to mean cumulative savings of $500 billion to the health economy.[23]

Federal investment has been key to this effort. As of 2006, according to the former director of NIH, the "estimated total cumulative investment at NIH per American over the past 30 years … is about $1,334 or about $44 per American per year over the entire period. In return, Americans have gained over six years of life expectancy and are aging healthier than ever before."[24] In fact, NIH investments in heart disease research, which amount to an average of $4 per year per American, have helped to cut the incidence of fatal heart attacks and stroke by more than 60 percent since 1975. Similarly, NIH-sponsored advances have improved survival rates for HIV patients, and economists estimate that the resulting savings to our economy will be close to $1.4 trillion for all past and future cohorts of infected individuals.[25] Instead of being an epidemic costing billions for new hospital beds and health care, AIDS is becoming a manageable outpatient disease, and HIV-AIDS victims are remaining productive in the economy.

In addition to benefiting the economy by improving health, NIH investments create direct and indirect economic gains by creating jobs and new goods and services. Families USA recently released a report that outlines the effect of NIH research dollars on individual states. The $23 billion that NIH invested in all 50 states in 2007

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[21] Nicole Maestas and Julie Zissimopoulos, "How Longer Work Lives Ease the Crunch of Population Aging," working paper, RAND Corp, Santa Monica, CA, Dec. 2009, http://www.rand.org/pubs/working_papers/2010/RAND_WR728.pdf.

[22] David Bloom, David Canning, and Mark Weston, "The Value of Vaccination," *World Economics* 6, no. 3 (July–Sept. 2005): 15–39, http://www.sabin.org/files/attachment/value_vaccination_bloom_canning_weston.pdf.

[23] Kevin M. Murphy and Robert H. Topel, "The Value of Health and Longevity," *Weekly Policy Commentary,* a publication of Resources for the Future (Sept. 28, 2009), http://www.rff.org/Publications/WPC/Pages/The-Value-of-Health-and-Longevity.aspx.

[24] Elias A. Zerhouni, "FY2007 Director's Budget Request Statement," presentation by NIH director to House Subcommittee on Labor, April 6, 2006, http://www.nih.gov/about/director/budgetrequest/fy2007directorsbudgetrequest.htm.

[25] Ibid.

generated over $50 billion in the production of new goods and services.[26] That means that every $1 million NIH invested in 2007 generated more than twice that ($2.21 million) in new state business activity. Furthermore, NIH grants in 2007 supported more than 350,000 jobs and the average wage of those hired for the new jobs was $52,000—significantly higher than the estimated average U.S. wage at the time, $42,000.[27]

NIH-supported industries, like the biopharmaceutical industry, offer another good lens for examining the impact of NIH funding on employment and wealth creation. According to a recent report, the biotech sector consistently outperforms others in job creation:

> Bioscience employment growth greatly outpaced national employment growth from 2001 to 2008. The bioscience industry added 193,748 jobs from 2001 to 2008, a hefty growth rate of 15.8 percent. This rapid rate of job growth was 4.5 times as much as the overall growth rate for the national private sector (3.5 percent).[28]

Clearly, the economic returns on basic biomedical research are significant and far outweigh the costs, especially when the effects of increased lifespan on productivity and national wealth are factored in.[29] A more inclusive analysis of costs and benefits thus provides a powerful economic argument for promoting convergence-driven research tailored to the 21st century. If the U.S. government invests in the research and technology infrastructure to further the convergence revolution, we can not only improve health care, but also strengthen the U.S. economy and American competitiveness.

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[26] *In Your Own Backyard: How NIH Funding Helps Your State's Economy* (Washington, DC: Families USA Foundation, 2008), p. 3, http://www.familiesusa.org/assets/pdfs/global-health/in-your-own-backyard.pdf.

[27] Ibid., p. 4.

[28] *Battelle/BIO State Bioscience Initiatives 2010,* (Biotechnology Industry Organization and Battelle Technology Partnership Practice, May 2010), p. ii, http://www.bio.org/local/battelle2010/Battelle_Report_2010.pdf.

[29] Kevin M. Murphy and Robert H. Topel, eds., *Measuring the Gains from Medical Research: An Economic Approach* (Chicago: University of Chicago Press, 2003).

3. NIH's Role in Advancing Convergence

We have already argued that convergence is the next revolution in biomedical research. The U.S. is the historic leader in biomedicine because of NIH's early investments in life science and education and because of the private-sector capital that followed. Now, with other countries eagerly duplicating the U.S. model of innovation in biomedical research, it is critical that NIH develop a vision to take us into the future. To do so, NIH needs consistent funding, greater willingness to fund seemingly risky research, and the infrastructure to capitalize on the next revolution in life sciences.

Funding Challenges and Low-Risk Research

The NIH budget nearly doubled between 1998 and 2003.[30] However, since then, NIH discoveries, which private investment builds on, have been affected by funding levels that are declining in real terms.

The enacted NIH budget for FY 2010 was $31.2 billion, a 2.27 percent increase from the previous year. However, the Bureau of Economic Analysis projected the biomedical research inflation metric (BRDPI) at 3.1 percent.[31] This means that the budget has not kept up with inflation (see graph), and that in constant dollars the budget actually shrank between 2003 and 2010.[32] Essentially, NIH's ability to fund current levels of research, let alone the emerging convergence revolution, decreased significantly.

In February 2009, the new administration's American Recovery and Reinvestment Act (ARRA) provided NIH with $10 billion in much-needed stimulus funding. However, this boost was a one-time funding opportunity, and it was available predominantly for already-filed grant applications, rather than new awards. Without a sustained source of increased baseline funding for NIH, and a

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[30] Data compiled by the American Association for the Advancement of Science, http://www.aaas.org/spp/rd/nihcht09.pdf (accessed July 24, 2010).

[31] "Biomedical Research and Development Price Index (BRDPI): Fiscal Year 2009 Update and Projections for FY 2010–FY 2015," memo from U.S. Department of Health and Human Services, Feb. 1, 2010, http://officeofbudget.od.nih.gov/pdfs/FY11/BRDPI_Proj_Feb_2010.pdf; and "The NIH Almanac—Appropriations," posting at the National Institutes of Health website, May 14, 2010, http://www.nih.gov/about/almanac/appropriations/index.htm (accessed Nov. 18, 2010)

[32] "The NIH Almanac—Appropriations," posting at the National Institutes of Health website, May 14, 2010, http://www.nih.gov/about/almanac/appropriations/index.htm (accessed July 24, 2010).

corresponding renewed focus on convergence, the U.S. cannot expect to retain its leadership in making biomedical advances.[33]

For several years, medical-research advocates have expressed concern that these declining investment levels will, over time, reduce research support, deter talented individuals from going into biomedical research fields, erode U.S. leadership in life science, and weaken our capability to tackle major health concerns.[34] We are now facing that reality. A recent *Nature* article notes that NIH is now funding fewer than one in five grant applications:

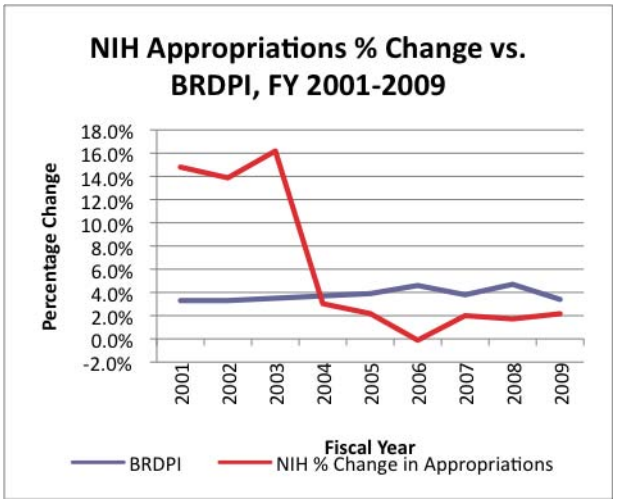

Figure 2: Change in the NIH's budget versus BRDPI, a metric that measures inflation in health care costs. Data Source: "Biomedical Research and Development Price Index (BRDPI): Fiscal Year 2009 Update and Projections for FY 2010–FY 2015," memo from the U.S. Department of Health and Human Services, Feb. 1, 2010.

> [In 2010], success rates for scientists applying for the agency's research-project grants have dipped to an estimated 19 percent, down from 21 percent in 2009 and far lower than the comfortable 32 percent of a decade earlier…The worsened odds partly reflect an increase of about 10 percent in the number of applications, many of which are recycled from failed stimulus grant proposals. In 2011 and 2012, the grant success rates are expected to fall further as stimulus funding runs out and its recipients attempt to extend support for their projects.[35]

As a result of decreasing grant success rates, scientists who peer-review NIH grant proposals have become more selective and more conservative when judging the merits of research projects.[36] In a well-understood phenomenon that affects all science research, a decline in grant approval rates pressures peer reviewers to demand more evidence for the eventual success of proposed theories before

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[33] Note: The proposed NIH budget for FY 2011 does meet the BRDPI metric. However, there is no cushion, and the final allocation is uncertain, given the difficult budget climate in Congress.

[34] Brown University et al., "A Broken Pipeline? Flat Funding of the NIH Puts a Generation of Science at Risk," statement by a group of universities and research institutions, March 2008, http://www.brokenpipeline.org/brokenpipeline.pdf.

[35] Meredith Wadman, "Francis Collins: One Year at the Helm," *Nature* 466, no. 7308 (Aug. 11, 2010): 808–810, http://www.nature.com/news/2010/100811/full/466808a.html.

[36] Ibid.

approving funding, which limits risk taking in the research portfolio. This inadvertently changes the way science is conducted by discouraging innovative, novel ideas in favor of more conventional approaches and incremental progress toward scientific discovery.

NIH needs a solid foundation on which to build a new convergence revolution with transformational implications for the U.S. research and development system. The inherent conservatism of peer review within the existing science support system, and the inconsistent funding base, hamper new approaches to research that must be embraced for America to maintain its competitiveness and innovative edge.

Convergence-Style Projects at NIH

Despite the challenges, convergence is slowly percolating throughout the scientific community. At NIH, convergence-style programs have gotten a boost from stimulus dollars and from the NIH Common Fund, created in 2006 to support cross-cutting research involving two or more of the agency's institutes and centers. In addition, convergence is gaining visibility through many of the initiatives that Francis Collins has promoted since becoming NIH director in August 2009.

In November 2010, Dr. Collins presented his five research priorities. These five pillars, as they've come to be known, are:

- high-throughput technologies
- translational medicine
- health care reform issues, including comparative-effectiveness research, disease prevention, personalized medicine, health disparities research, pharmacogenomics, and health research economics
- global health issues, and
- reinvigorating and empowering the biomedical research community.[37]

As part of his effort to make progress in these areas, Dr. Collins held the "Big Think" meeting in May 2010 to consider innovative ideas for Common Fund or other NIH support. Coincidentally, this meeting focused on the three pillars most relevant to convergence: application of high-throughput technologies, translation of basic research into diagnostics and therapeutics, and utilization of science to benefit health care reform.

In an effort to break beyond the current paradigms, nontraditional stakeholders from the science community outside of NIH were invited. Presenters discussed a broad array of promising areas, including, for instance, metabalomics and its

[37] Francis Collins, "Opportunities for Research and NIH," *Science* 327 (Jan. 1 2010): 36–37.

applications for clinical medicine. In addition, all attendees were offered the opportunity to submit one-page memos on "big ideas" for NIH. Interestingly, the format for these memos followed the "Heilmeier questions" formulated by George Heilmeier, a former director of the Defense Advanced Research Projects Agency, indicating that Dr. Collins is serious about bringing new ideas into NIH.

"Progress can be quick when researchers with different knowledge bases are encouraged to come together."

With Dr. Collins at the agency's helm, it may not be surprising that projects that blend seemingly unrelated disciplines are gaining some support. While there is still much more to do, two examples of convergence-style research at NIH are worth highlighting: The Cancer Genome Atlas (TCGA) and Therapeutics for Rare and Neglected Diseases (TRND).

The Cancer Genome Atlas (TCGA): Targeted Therapeutics for Cancer Subtypes

The Cancer Genome Atlas (TCGA) is a comprehensive and coordinated effort to accelerate understanding of the molecular genetic basis of cancer through the application of genome analysis technologies. These technologies include next generation sequencing platforms and nanopore technology, and other advances requiring the integration of engineering with biochemistry, chemistry, bioinformatics, nanotechnology, and physics. As a joint effort of the National Cancer Institute (NCI) and the National Human Genome Research Institute, TCGA cuts across institutional lines as well as scientific disciplines.

Begun in 2006, TCGA is already yielding important new findings. TCGA investigators recently discovered that the most common form of malignant brain cancer in adults, glioblastoma multiforme (GBM), is not a single disease but instead appears to comprise four distinct molecular subtypes. Researchers also found that response to aggressive chemotherapy and radiation differed by subtype. Aggressive treatment was most effective for patients with one particular subtype, who appeared to succumb to their disease at a rate approximately 50 percent slower than patients treated with less aggressive therapy. The effect was less pronounced for patients with two of the other subtypes, and it was not present at all for patients with the fourth subtype. These results may lead to more personalized approaches to treating groups of GBM patients based on their genomic alterations. The study, published in *Cancer Cell*, provides a solid framework for investigating targeted therapies that may improve the prognosis for patients with this cancer, which is nearly always fatal.[38]

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[38] R. G. Verhaak et al., "Integrated Genomic Analysis Identifies Clinically Relevant Subtypes of Glioblastoma Characterized by Abnormalities in PDGFRA, IDH1, EGFR, and NF1," *Cancer Cell* 17, no. 1 (Jan. 19, 2010): 98–110. For an NCI news release about the findings, see http://cancergenome.nih.gov/media/glioblastoma4subtypes.asp.

As TCGA's discoveries about GBM illustrate, progress can be quick when researchers with different knowledge bases are encouraged to come together. As convergence-style research stretches beyond genomics and becomes more commonplace throughout NIH and in other agencies and academic centers, the advances and societal benefits that are sure to follow will further demonstrate the value of investing in more integrated research.

Therapeutics for Rare and Neglected Diseases (TRND): Bridging the Valley of Death for Global Health

The Therapeutics for Rare and Neglected Diseases (TRND) program began in 2009 at the (NIH) Chemical Genomics Center (NCGC). TRND investigators utilize high-throughput technologies (robotics, data processing and data-control software, liquid-handling devices, and sensitive detectors) to quickly conduct millions of biochemical, genetic, or pharmacological tests on small molecules that hit disease-modifying targets. The results, a library of organic compounds of this class, are often candidates for use as pharmaceuticals or targeted therapeutics.

The TRND program focuses on discovering drug targets for rare and neglected diseases affecting, in aggregate, a large population around the globe. Since rare and neglected diseases are without a strong economic market, TRND's goal is to investigate drug targets for these diseases to the point where it makes economic sense for industry to develop the drug. In this way—by investing in basic research for drugs that for-profit corporations would not otherwise fund, and then handing off those drug targets to be developed and commercialized in the private sector—NIH is paving the way for new treatments.[39]

In the short time the program has been running, investigators have discovered a potential compound that might be the basis for treating schistosomiasis, also known as bilharzia or snail fever. This disease affects 207 million people worldwide and kills 250,000 each year. Public-health experts are concerned that the Schistosoma parasites will become resistant to a current drug of choice, praziquantel, which will then lose its effectiveness—as has been the case with agents used to combat malaria, tuberculosis, and many other infectious diseases. Alternative drugs are thus potentially of great value, not only to the 70 tropical nations where these diseases are prevalent, but also to foreign-aid donors like the U.S.

By incorporating computer science, engineering, pharmacology, and biology into one concerted effort, TRND is approaching solutions to some of the world's most overlooked medical conditions. Perhaps more importantly for the convergence model, the TRND program is promoting a new kind of collaboration among a broad network of actors that cuts across traditional research structures, public-private partnerships, and disciplines.

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[39] For more information, see "Frequently Asked Questions" at the NIH Office of Rare Diseases Research website, http://rarediseases.info.nih.gov/files/TRND_FAQs.pdf.

Implications for the Future

The convergence revolution is a smart investment if we are to keep our biomedical research the finest in the world, and if we are to extend progress in other scientific areas as well. The convergence model offers a vision for NIH that will once again capture the imagination and also justify consistent and progressive funding of the agency.

Providing adequate financial support for interdisciplinary research is key, but we must also encourage investigation that crosses existing boundaries. While NIH is perhaps the most likely locale for dramatic convergence-driven advances, all federal agencies should work toward shared goals by embracing not only interdisciplinary collaboration but also cross-agency collaboration. Fortunately, Congress already recognizes the importance of such interaction. In a 2009 report, for example, the Senate Appropriations Committee stated:

> The Committee applauds the successes which have been achieved when the Department of Energy has collaborated with the National Institutes of Health [NIH]. These successes include the human genome project, advances in bioinformatics, and breakthroughs in atomic resolution structural biology. The Committee strongly encourages the DOE Office of Science and the National Laboratories to reach out to the NIH to institutionalize senior level contacts with the goal of identifying opportunities for sustained collaboration in research and development. The Committee notes that long-lasting relationships are necessary to build the types of integrated collaborative programs that could bring about breakthroughs in biomedical imaging, systems biology, and other key areas of research.[40]

[40] Senate Appropriations Committee, *Energy and Water Development Appropriations Bill, 2010,* report, 111th Cong., 1st sess., Committee Print 111-45:104, http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=111_cong_reports&docid=f:sr045.111.pdf.

4. Recommendations

As we've explained, the recent revolutions in molecular and cellular biology and in genomics continue to make crucial contributions to medical knowledge and health care. To capitalize on those advances, we now need to heed the calls for a new, integrated research model and support a third revolution, the convergence of the life, physical, and engineering sciences. Several important strategies are outlined below.

1. Ensure that Congressional funding meets or beats BRDPI, NIH's biomedical research inflation metric, annually.

For the past several years, annual NIH funding levels have failed to keep up with the NIH biomedical research inflation metric (BRDPI). Budgetary strains, coupled with an already conservative peer-review system, mean that innovative research approaches are likely to go unfunded in favor of more predictable, incremental research.

Consistent funding levels will allow NIH to plan and incorporate a more promising and diversified-risk research portfolio. In addition, in times of economic recession, when beating the BRDPI may not be possible, funding for extramural grants and flexible funding programs like the Common Fund should be protected as the last in line for cuts.

2. Establish a convergence ecosystem by building connections across stovepiped systems.

Scientific research has historically been funded in separate stovepipes by science-mission agencies, including the National Science Foundation, the Department of Energy, the Department of Defense, and the National Institutes of Health. In areas where collaboration can be highly productive, our funding agencies, not just our scientists, should become collaborators. That means talking to one another, jointly identifying the areas of greatest opportunity as well as the top scientific challenges, and developing common strategies for progress.

Some interagency research does take place, but such projects seem to depend on informal friendships or on slowly established working relationships between individuals in various agencies. Mechanisms to enable and foster such connections need to be institutionalized.

The NIH Challenge Grants, which are available to investigators from outside NIH, are a good first step. The next step might include increasing opportunities for

experienced federal agency researchers to take on short-term assignments in other research agencies. For example, think-tank environments could be established within each research agency, and agency detailees from across the executive branch could be invited to visit for several months and collaborate on the research priorities of the host institution. This might be coordinated by the National Science and Technology Council.

We also suggest that the Office of Science and Technology Policy include convergence as a critical enabling scientific model in a Cabinet-wide initiative on the larger biology economy. This effort would help coalesce convergence experts and expose research opportunities, much as the National Nanotechnology Initiative (NNI) and the High Performance Computing and Communications (HPCC) effort have coordinated and spurred activity in nanotechnology, and computing respectively.

3. Reform peer-review processes to support interdisciplinary grants.

Peer review at NIH has long played a critical role in the success of the U.S. research enterprise in terms of both enabling medical advances and supporting the biomedical economic sector. However, an increasingly conservative peer-review system will lead to missed opportunities.

NIH has recently initiated an effort to reform its peer-review process and protect its ability to undertake cutting-edge, higher-risk research, which tends to receive less emphasis when overall research funding is in decline. What is still needed is academic enrichment of the peer-review teams, to increase both cutting-edge disciplinary depth and the array of disciplines represented. This will enable more immediate awareness of promising, convergence-style research that requires a group of nontraditional collaborators incorporating experience in computing, nanomaterials, genomics, imaging, and other evolving systems and applying that cumulative understanding to a biomedically oriented research mission.

Certain efforts that have already started should be institutionalized and expanded. These include the development and utilization of a College of Scientific Reviewers in every NIH institute and center. These bodies are review boards composed of respected scientists from outside NIH. With the help of modern technology, the members can review proposals and offer recommendations from their offices across the country, rather than having to travel to NIH headquarters in Bethesda, MD. Widespread use of such review boards across the NIH campus will bring together cutting-edge expertise and facilitate the funding of convergence-style projects.

There may be additional ways to adapt the existing peer-review system for convergence. To explore the possibilities, a group of experts in the NIH peer-review process should be brought together.

4. Balance large-scale efforts with smaller grant projects.

Individual investigator, RO1-style grants for smaller projects are a time-honored, respected tradition. Small projects often lead to innovation and new discoveries, and support for them should continue. At the same time, it is vital to also direct resources to large-scale projects that include multiple principal investigators. These undertakings allow researchers from many disciplines to conduct systematic inquiries into general target areas while pursuing their own specific interests.

Since collaboration and innovation in research methods are more difficult if individual researchers are isolated in separate departments at their institutions, we suggest the founding of convergence centers at institutions across the country that would include multiple principal investigators. A group of agency and academic experts should convene and use a systems approach to design these centers around national research priorities.

5. Improve interdisciplinary research among the 27 NIH institutes and centers.

NIH evolved following World War II in response to an assumption that the pathway to medical solutions for each disease would be unique to that disease. However, the molecular and genetic revolutions have taught us that cross-cutting research can produce advances that will affect many diseases. NIH's disease-centered model was not organized to accommodate this approach. Each of the agency's 27 institutes and centers (ICs) has its own research agenda and tends to operate autonomously.

Since 2006, the NIH Common Fund has supported trans-NIH research, but this effort needs to be broader. The current mechanisms for ICs to collaborate on multidisciplinary grants should be reexamined, and a more effective system should be devised. Meanwhile, the Common Fund can be an initial tool to encourage convergence research in promising areas.

6. Educate, expand, and support the next generation of convergence researchers.

Universities increasingly understand that the merger of scientific and engineering fields is a reality and will be the future of the life science enterprise. New efforts need to be undertaken to educate the next generation of researchers to work in cross-disciplinary fields. While a deep disciplinary background remains vital, including a robust cross-disciplinary education is essential additional preparation for our future scientists and important for research careers.

One recommendation is to offer more research training grants to encourage institutions to develop new courses/programs that prepare students, postdoctoral researchers, and fellows for convergence-driven research. This means creating new curricula, apprenticeships, and training programs to enable cross-disciplinary expertise.

In addition, we must strengthen the pipeline of future researchers by addressing the diversity problem in our educational system. According to a recent report, only 19 percent of young people from families with incomes below $25,000 obtain a community college degree or higher, compared with 76 percent from families with incomes of $76,000 or more.[41] It is clear that we are missing out on a large pool of potential talent. We need to continue efforts to engage a broad range of young people in Science, Technology, Engineering, and Math (STEM) fields.

To that end, careful consideration should be given to the recommendations contained in two recent studies. One is a 2009 report by the Council on Graduate Schools, titled *Broadening Participation in Graduate Education,* which outlines ways to identify and cultivate talented students from groups that are traditionally underrepresented in science and engineering graduate programs. The other report, *Gender Differences at Critical Transitions in the Careers of Science, Engineering, and Mathematics Faculty* (released by the National Academies in 2010), suggests specific strategies for achieving gender equality on the STEM faculty career path.

In addition to efforts encouraging young people to pursue STEM careers, legislation is needed to enable America to draw and retain brilliant researchers from across the globe. For example, an enhanced H-1B Visa (Professional in a Specialty Occupation) would enable talented non-Americans educated at our finest institutions to find a path to citizenship while they work to enhance our economy and our innovation ecosystem.

[41] Paul Osterman, "College for All? The Labor Market for College-Educated Workers," report for the Center for American Progress, Aug. 2008, http://www.americanprogress.org/issues/2008/08/college_for_all.html.

CLOSING

The merger of the life, engineering, and physical sciences promises to fundamentally alter and speed our scientific trajectory. NIH and other affected agencies, if adequately funded and made ready, can be thought leaders in this next scientific revolution. The time is right for NIH and other agencies to take up convergence as the wave of the future, creating dramatic new opportunities in medicine for new therapies and diagnostics, economic opportunity, as well as promise in many other scientific fields, from energy to climate to agriculture.

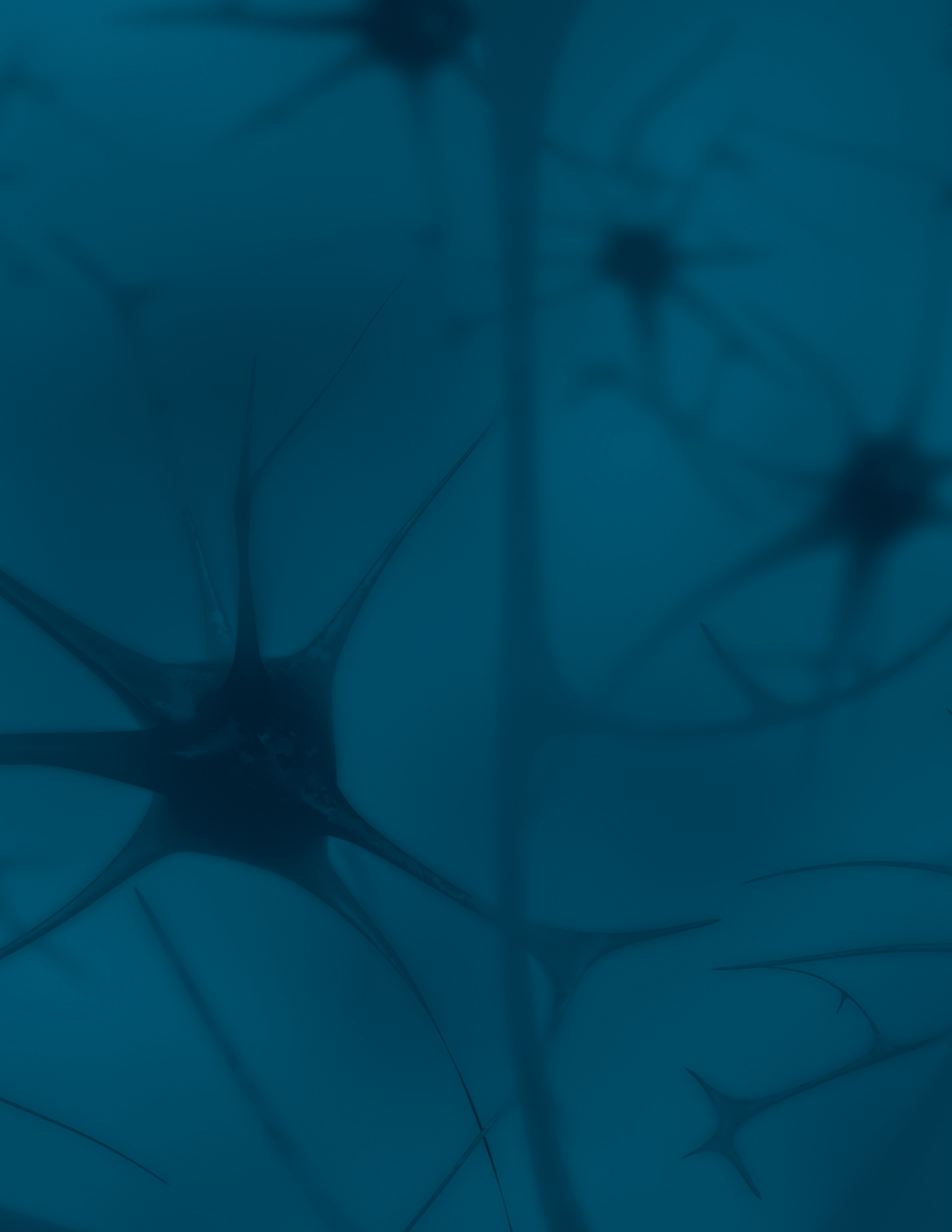
For more information about this report,

contact the MIT Washington Office:

820 1st St. NE, Ste. 610

Washington, DC 20002

202.789.1828 || 617.324.9981



Massachusetts Institute of Technology
Washington DC Office
820 First Street NE, Suite 610
Washington, DC 20002

202-789-1828

http://web.mit.edu/dc/

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