Convergence: The Future of Health
Cover image: The lungs are one of the major sites of metastasis—the spread of malignant tumor cells to distant organs. To help protect the lungs (blue) from this deadly process, bioengineers have created microscopic drug depots (red) to focus the effect of anti-cancer drugs that may have limited or toxic effects when delivered to the whole body. In the future, these microparticles could be administered with technology as simple as an inhaler, buying the body time to build up resources to fight or prevent this fatal migration.

Image credit: Gregory Szeto, Adelaide Tovar, Jeffrey Wyckoff, Irvine Laboratory, Koch Institute at MIT
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Dear Colleagues:

Humankind faces serious challenges in overcoming diseases, mitigating the rising costs of healthcare, and reducing health disparities. While Convergence cannot single-handedly solve these challenges, it will play a key role in accelerating progress in health and healthcare through research innovations.

Faculty members and participants from many universities, organizations, and firms came together to contribute to the development of this report. We now present it to the research and policy communities to illustrate the power and potential of Convergence research to improve health and healthcare through the integration of engineering, physics, computation, and life sciences.

Despite the incredible promise Convergence holds for advancing novel approaches to therapies, health analytics, drug delivery, diagnosis, and disease prevention, Convergence faces major barriers limiting its full potential to bring new and exciting health innovations to patients.

We hope this report, which builds upon findings from previous reports, will form the beginning of a multifaceted research strategy and highlight the many innovative opportunities made possible by Convergence. The report was drawn from a series of meetings with colleagues from across the country and from diverse stakeholders from academia, government, industry, and philanthropy. We hope that its descriptions and recommendations will amplify the dialogue so that Convergence research strategies can advance at the campus and national levels.

We look forward to your thoughts and questions.

Sincerely,

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June 2016
As report Co-Chairs, we take full responsibility for the content of this report. We also thank the many people who have contributed to thoughtful discussions and given sage advice on this project. Participants in two workshops contributed many stimulating suggestions and provocative results. Some sections of the report have been read by Advisors and Workshop Participants, but its final content is the responsibility of the Co-Chairs. We thank the Advisors, Workshop Participants, Writers, Research Assistants, and Staff for their valuable assistance in this project.
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The life sciences are in the midst of a revolution. Scientists are inventing ways to regenerate lost limbs and replace malfunctioning organs. Genomics and Big Data are being used to tailor treatments for patients’ needs. Therapies to correct disease-causing genetic defects are now in clinical trials. Increasingly, patients play critical roles in their own care, from monitoring their health with wearable devices to shaping the direction of research on the diseases that affect them.

The technologies driving these and other biomedical breakthroughs go well beyond health care. They impact food, energy, and the environment to improve the lives of millions—if not billions—of people. This revolution—called “Convergence”—is creating jobs, speeding products to market; improving agriculture, defense, the environment, and energy production; and helping to grow America’s gross domestic product (GDP). The Convergence Revolution promises to enhance quality of life worldwide.

Convergence comes as a result of the sharing of methods and ideas by chemists, physicists, computer scientists, engineers, mathematicians, and life scientists across multiple fields and industries. It is the integration of insights and approaches from historically distinct scientific and technological disciplines. Convergence is a broad effort across the sciences that will play a crucial role in many fields of endeavor. As noted above it needs to be applied to help solve many of the world’s grand challenges. This report specifically focuses on one of these challenges: improvement of health.

Despite its promise, however, the Convergence Revolution is constrained by challenges in education, industry, and government, as well as a severe shortage of research funding designed to support its unique cross-disciplinary nature.

To overcome the world’s most pressing health problems and remain competitive in a global economy in which Convergence technologies are increasingly driving growth, the U.S. must step up its efforts to meet these challenges. This nation must do everything possible to accelerate Convergence research.

This report shows that an accelerated Convergence research strategy can lead to truly major advances in fighting cancer, dementia and diseases of aging, infectious diseases, and a host of other pressing health challenges. Convergence is already showing dramatic progress toward more powerful imaging technologies; nanotechnology for diagnostics and drug delivery; “silencing” cancer genes; re-growing injured body parts, and unraveling the complexity of diseases.

A 2011 report from the Massachusetts Institute of Technology (MIT), The Third Revolution: The Convergence of the Life Sciences, Physical Sciences, and Engineering, made the case that Convergence is not only important for life science research and health care, but is also critical for future revolutionary advances in many fields. Subsequent meetings and reports from the National Academy of Sciences, the American Association for the Advancement of Science, and federal agencies have explored Convergence from a variety of contexts, such as university structure, nature of interdisciplinary research, and support for collaboration in teams. This report builds on these prior studies.

The growing acknowledgment of the promise of Convergence is apparent from the large number of new research initiatives launched by leading academic institutions and in the increasing amount of private-sector investments in innovations created by Convergence science.

However, delivering on the full promise of Convergence is hindered by federal research funding practices that often reflect a classical, disciplinary-based structure. This structure harkens back to a time when life science, physical sciences, and engineering were viewed as separate activities—before the sequencing of the human genome, before the advent of Big Data analytics requiring sophisticated mathematical and computational algorithms, and before novel, complex materials had been developed for use within the human body.

Despite recent federal programs such as the Brain and Precision Medicine Initiatives (see box on page 13), which are Convergence in nature, in fiscal year (FY) 2015, less than 3 percent of National Institutes of Health (NIH) funding was
allocated to principal investigators in engineering, physical science, or math/statistics.

Among federal agencies, the National Science Foundation (NSF) is the primary source of support for basic engineering and physical sciences, but the level of funding in the convergence of these disciplines with biomedical science is minuscule.

Although other federal agencies such as the Department of Energy (DOE), the Defense Advanced Research Projects Agency (DARPA) and the Department of Agriculture (DOA) are beginning to recognize the promise of Convergence, to date, no federal agency or office has the primary responsibility to promote the convergence of engineering, physical, computational, and mathematical sciences with biomedical sciences.

This report goes far beyond the 2011 MIT report. It both documents the breadth of opportunities with huge biomedical payoffs now within reach and outlines initial research strategies for achieving those payoffs.

By beginning to systematically map such opportunities and the relevant technologies, this report makes the case that explicit Convergence strategies for research funding on the part of federal agencies—and explicit strategies to facilitate Convergence research implementation on the part of universities—are both possible and overdue.

Specifically, this report:

**Documents the increasing humanitarian and fiscal costs of healthcare.**

Nearly half of adults in the U.S. suffer from non-infectious chronic diseases such as cancer, stroke, diabetes, and heart disease; one in four adults has two or more chronic conditions. Anxiety disorders and depression are common co-factors, lowering productivity and quality of life. With an aging population, the incidence of Alzheimer's disease and other dementias is rising rapidly, putting huge financial and emotional burdens on individuals and families. Chronic conditions not only cause 70 percent of deaths, they also account for more than 85 percent of U.S. healthcare costs. The growing incidence of obesity, attributable to unhealthy diets and lifestyles, promises to exacerbate these trends. The result is more than $3 trillion per year—17.5 percent of GDP—in national healthcare expenditures; this amount is projected to rise to over 19 percent of GDP by 2024. Without significant breakthroughs in early diagnosis, prevention through lifestyle changes or other interventions, plus novel lower-cost diagnoses and treatments—precisely what Convergence research offers—these healthcare fiscal trends will continue to undermine our national competitiveness.

**Analyzes a number of unmet needs and emerging Convergence solutions.**

How could Convergence strategies—applied systematically—impact healthcare? A first look at high-priority opportunities might include:

- **Cancer.** Current diagnostic methods are often expensive and insufficiently accurate, and current therapies are largely limited to surgery or treatment with toxic chemicals or radiation. Convergence strategies offer new approaches, including minimally invasive methods of early detection, when treatment is far easier. These include urine tests that use nanoparticles designed to interact with cancer cells and release easily detected synthetic biomarkers, and blood tests that capture DNA from tumor fragments and then analyze it with novel sequencing technology.

Once cancer is detected, new drug delivery methods can deliver multiple drugs to a cancer, or deliver two different therapies in a controlled “one-two punch,” or deliver fragments of RNA that turn off or “silence” a cancer gene. Nanotechnology-based cancer vaccines chemically link albumin, a normal blood protein, to transport cancer antigens directly to lymph nodes, boosting the effective tumor-fighting power of the body’s immune system while...
minimizing the impact on other tissues. Novel designs can permit nanoparticles to penetrate the brain and attack tumor cells there.

Convergence offers important advantages for cancer immunotherapy, which uses a new class of drugs called “checkpoint inhibitors” to redirect the body’s immune system to recognize and kill tumor cells. While enormously exciting, this new therapeutic strategy only works for some cancers and for only some patients. More research is needed to understand the biochemical and genetic background that predict success. A promising enabling technique is a method of identifying specific cellular characteristics with antibodies labeled with multiple, distinctive heavy ions. The complex set of data generated by this approach can be used to personalize immune therapies, hastening the time when the body’s immune system will be the weapon of choice against cancer.

• Infection and Immunity. Synthetic biology is a Convergence strategy that designs and introduces new genetic circuits in living cells. It is rapidly transforming the way we approach infection and is opening up fundamentally new ways of monitoring and modifying the properties of living cells. It offers entirely new strategies to eliminate disease vectors such as mosquitoes, to enlist modified bacteria in the gut as living sensors against disease, and even to create “smart” probiotics that could both identify and attack infectious agents.

More broadly, synthetic biology tools give researchers the potential means to monitor a wide variety of phenomena in living cells and use that information to modify the cell’s activity, for example by initiating or shutting off production of a protein. In one experiment, scientists inserted 12 different switches, each controlling a different cell function, into a single living cell.

Even before these powerful tools are applied to specific diseases, however, they are likely to enable a whole new set of low-cost diagnostic tools that could be rapidly deployed against new epidemics such as Zika or Ebola, or used to detect the presence of antibiotic-resistant germs in hospitals. Already, researchers have taken engineered biological circuits out of cells and freeze-dried them on paper strips, creating field-ready diagnostics similar to a pregnancy test that turn color upon contact with a particular pathogen. In one demonstration of the potential, a team of scientists created 20 different paper-based sensors for Ebola within 24 hours.

• Brain disorders and injuries. Use of modern IT-based sensors, smart devices, and sophisticated software apps are making it possible to measure and quantify behavior as never before. New screening tools for autism and cognitive impairment have the potential to enable early diagnosis and intervention in infants. New non-invasive methods of gently stimulating specific brain circuits in aging adults, coupled with brain training exercises, show promise for improving short-term memory. Similar stimulation methods are being tested to “wake up” neural patches inserted to repair damaged brain circuits, an approach that might one day be used to treat traumatic brain injuries.

New methods of seeing deep into the brain—based on chemical engineering techniques—are helping researchers build more detailed 3D maps of neural circuits. These maps have already enabled researchers to identify brain cells related to a particular memory, and may enable stimulation methods to recover lost memories in Alzheimer’s patients.

Massive genetic sequencing and sophisticated data processing have led to the identification of subtle genetic differences in people with schizophrenia. This approach may provide effective biomarkers for the early diagnosis of a range of neuropsychiatric disorders that are now diagnosed only subjectively, after symptoms appear. Still in development are technologies that could monitor the electrical dynamics in a cluster of neurons and then map...
those dynamics to specific behaviors, or that could measure facial or vocal expressions to assess behavioral intent.

• **Heart disease, diabetes, inherited genetic disease.**
  Wearable or implantable sensors could potentially provide early warning of heart attacks or stroke, while also generating large datasets that could help optimize therapies. Patient-friendly technologies such as wearable blood sugar sensors or “smart” insulin that responds automatically to blood sugar levels would help patients with diabetes manage their disease. Advanced genetic profiling, including new high-throughput methods of mapping the epigenome, could not only lead to early diagnosis of inherited genetic diseases but also lay the foundation for rewiring the genes causing the diseases.

Even this preliminary overview suggests that Convergence strategies have remarkable potential for many health challenges: in disease prevention, in earlier and better diagnosis, in new therapies and better drug delivery, and in wholly new possibilities enabled by Big Data insights. It may even wipe out whole categories of disease.

**Illustrates four Convergence approaches and their enabling technologies.**

The report provides examples of specific Convergence strategies that could have a broad impact on next-generation diagnostics and therapies and thus on the future of health in the United States and globally. It describes four specific approaches, among a vastly larger set, with particular promise:

• **Imaging.** Visualizing structures and processes inside the body has become one of the most fundamental technologies in medical practice. However, better diagnostic potential requires higher resolution to see individual cells or cellular components and also for greater depth of visualization through the body’s tissues. Several new techniques allow high throughput imaging at the molecular level, using antibodies tagged with specific ions to identify specific proteins or genes, or using two complementary methods to detect RNAs at the genomic scale in cells to determine which genes are active in which cells.

  Two new methods of whole body imaging draw on chemistry, materials science, applied physics, engineering, and computational science to create new windows into the body. Raman spectrometry uses subtle properties of scattered light to image molecular interactions in cell populations with high sensitivity and high resolution, with promise for the detection of breast cancer. Photoacoustic imaging uses a laser to pulse light into the body, heating up molecules that create pressure waves that produce sound, which can be converted into an image. It is being tested in animal models and people for detecting cancers and degenerative eye diseases such as diabetic retinopathy, macular degeneration, and glaucoma.

  Whole organ imaging is now possible by infusing organs with a gel that transforms into a plastic matrix that holds important biomolecules in place. Detergents then dissolve and extract opaque matter, leaving an intact but optically transparent organ. This technique has already been applied to the brain—one of the most architecturally complex and, therefore, least understood organs—but it can be applied to all organs.

• **Nanotechnology.** Nanotechnology is fundamentally about fabricating very small things—particles so small that thousands could fit on the period at the end of this sentence—and hence small enough to be carried around the body in the blood stream. Sophisticated engineering and materials science can create complex tiny “nano” packages to carry drugs or other therapies to specific targets in the body. Such packages can detect disease or even directly kill cancer cells with minimal side effects. Clinical trials are already underway for their use in the liver and brain, and for cancer, with enormous potential for a wide range of applications.
Specific uses under development include nanoparticles carrying RNA fragments that can turn off or silence a specific gene, and coating the nanoparticle with cell fragments or other materials that camouflage it from the body’s immune system and thus allow it to target a wide range of organs or tissues. The different coating could enable nanoparticles to slip through the blood-brain barrier and deliver a wide range of therapies to the brain.

Nanoparticles have a powerful potential for treating cancer. Decorated with cancer-specific homing molecules, the impact of the drug or therapy it carries could be restricted to cancer cells, limiting damage to healthy cells. Nanoparticles can carry multiple drugs, releasing them in sequence, if needed, or targeting several cancer genes simultaneously. Mechanical approaches have also been suggested. For example, a nanoparticle that contains a magnetic disk, upon reaching a cancer cell, could be rotated by an oscillating magnetic field to kill the cancer cell.

• **Regenerative engineering and medicine.** Regenerative engineering combines advanced bio-engineering with the development of advanced materials compatible with the body. Wearable bioreactors could be designed to enable tissue regrowth, and 3D printing of living cells might be used to produce new tissues. The goal is to dramatically improve quality of life for wounded military personnel, aging seniors, and all those with damaged or dysfunctional body parts. Already techniques to re-grow torn ligaments and tendons are in clinical trials. The distant promise is to re-grow more complex tissues, such as a limb or a whole knee.

With more than 100,000 people in the U.S. on waiting lists for organ transplants, there is a pressing need for replacement organs. Work is also underway to grow whole organs—such as livers, kidneys, or hearts—for transplant. The process starts with adult stem cells from the patient (found in fatty tissue or even ordinary skin cells reprogrammed to act as stem cells) that are loaded into a 3D printer cartridge and “painted” onto a collagen structure of the desired organ obtained from a cadaver or a pig. The result would be an organ that is immunologically identical to the patient, without the risk of tissue rejection.

Another, perhaps simpler, approach leverages the redundant capacity of the human body. Organs like the kidney or liver can provide sufficient function even with only 10-20 percent of their normal capacity. A wedge of healthy organ tissue, grown from the patient's cells, could be inserted into a failing kidney or liver and stimulated to integrate into the native organ. This could keep patients alive and provide a higher quality of life than currently available in treatments such as dialysis. Achieving regenerative engineering goals will simultaneously advance basic understanding of the developmental process that generates the organ during development, including identifying the signaling processes that direct stem cells to form complex tissues.

• **Big Data and health IT.** Human health depends on our genetic heritage, but just as critically on environmental and behavioral factors—what we are exposed to, what we eat, our lifestyle choices. Compared to the wealth of data about our genes that is now available, there are no molecular-level reference databases about environmental exposures or behavioral influences on health and wellbeing. The prevalence of smart devices makes it possible to begin to collect such data, either through voluntary consumer input of data or collected by wearable or implantable sensors. Apps to do just that for research purposes (with consumer consent) are being developed, and consumers in large numbers are already volunteering their data. The convergence of smart mobile devices, increasingly powerful sensors—that can detect genetic syndromes from facial recognition software or test for Parkinson’s disease from vocal patterns—and machine learning algorithms have the potential to improve medical diagnosis and decision-making.
High throughput techniques combined with advanced mass spectrometry could assess individual exposures to environmental health factors. A blood sample contains a record of exposure to prior infections, to environmental antigens and toxins, and to nutritional metabolites from our diet. Creating a database of these biological markers of the “nurture” contribution to human health and correlating it with genetic databases that define our “nature” could link an estimated one million biomarkers to their environmental causes, creating a map of the chemistry of life as it is actually lived. Machine learning algorithms could then reveal predictive patterns, ultimately constructing an empirical basis for personalized prevention and treatment.

The potential to gather, compare and relate genetic, environmental, and behavioral data gathered from millions of people could transform our understanding of health and wellness for the benefit of all humanity.

Reviews challenges that constrain Convergence from reaching its potential to improve health and healthcare.

Challenges include diminished federal research funding, siloed agency structures and missions, and disciplinarily-restricted grant review mechanisms that make it difficult for the Convergence Revolution to reach its full potential. From 2004 to 2015, biomedical R&D funding has declined by 22 percent and, even with recent increases, the NIH budget is still lower than it was before 2003 in inflation-adjusted dollars. Federal investment in basic research—the early stage funding that is the fundamental building block for innovation and economic advancement—has diminished steadily from 2002 to 2013. While federal investment in Convergence research has grown slightly, it remains far below what is needed to realize its potential to revolutionize healthcare.

Funds allocated specifically for biomedical Convergence research are far too limited—in part because while Convergence opportunities overlap the missions of many agencies, it is the central focus of none. Even tracking such funding is difficult: there is no “Convergence” category for grant applications or data on whether co-principal investigators are based in different academic departments (as is almost always necessary in Convergence projects by their very nature). The available data indicate that, while NIH grants to departments of engineering and bioengineering increased fourfold between 2000 and 2014, only a small percentage of total NIH funding, probably about 3 percent of award dollars in FY2015, went to all principal investigators working in the fields of engineering, computer science, mathematics, and physical science, combined.

The funding process also creates a barrier. We cannot blend insights and skills from the engineering, physical, biological and clinical sciences into a unified whole when review panels for grants do not include the relevant expertise. At the least, agencies should develop explicit Convergence guidelines and parameters to guide review panels.
Industry, too, faces challenges in the adoption of Convergence. For example, the common “blockbuster drug” economic model does not fit personalized therapies or many Convergence technologies. Many companies have limited Big Data analytic capability, even while confronting massive amounts of new data. As Convergence approaches become more prominent, industry faces a shortage of workers with appropriate skills.

That shortage of talent is attributable to challenges at the university level. The academic structures of most colleges and universities are not yet well positioned for Convergence research. Nonetheless, many institutions have recognized this emerging trend and have developed a growing number of cross-disciplinary centers for research and teaching. However, few students are being trained for the growing number of opportunities in Convergence fields. The U.S. Bureau of Labor projects significant growth over the next decade in the demand for talent in bioengineering, computer and information science, and statistics. It is clear that the U.S. educational system needs to train more students with knowledge in multiple scientific and technical disciplines. Disciplinary depth must be retained and combined with modern IT and computational skills; new academic strategies are required to draw more disciplines to the opportunities in biomedical science.

Recommends that government agencies, academia, and industry launch a detailed strategy-development process.

A key recommendation is for a sustained, steady increase in the NIH budget to enable at least 20 percent of the agency’s research to be targeted at Convergence research, without detriment to other research budgets.

Increases in research spending are also needed at NSF, DOE, and DARPA to enable them to continue to play a significant role in advancing Convergence.

A second key recommendation is to create a Convergence Working Group across NIH and other federal agencies and to task this group with developing both a Convergence research strategy—of the type suggested in this report—and with identifying promising opportunities for such research. This effort should include a new external advisory committee of Convergence experts; the advisory committee might also be asked to conduct a far-reaching study, with input from both academia and industry, on the next frontiers of Convergence research to help prioritize research opportunities.

Sets out a vision for the future.

This report suggests numerous ways in which Convergence research will have a transformative impact on health and healthcare practice, with significant savings in both human suffering and fiscal health expenditures. Convergence will also advance basic knowledge of human biology. The report suggests focusing the power of U.S. research capacity—in engineering, physical science, mathematical and computational science, together with life science—on achieving these goals over the next decade. This effort has the added benefit of training a generation of scientists and engineers across disciplines to take full advantage of the opportunities that Convergence research holds. This report proposes an initial framework for a strategy—in a series of critical disease and technology areas—that a concerted effort by federal agencies, universities, foundations, and industry could build over time into a true road map for Convergence.
This report proposes an initial framework for a strategy—in a series of critical disease and technology areas—that a concerted effort by federal agencies, universities, foundations, and industry could build over time into a true roadmap for Convergence.
Chapter 1: Introduction

Convergence Defined
Convergence as applied to health is an approach to problem solving that integrates expertise from life sciences with physical, mathematical, and computational sciences, as well as engineering, to form comprehensive frameworks that merge areas of knowledge from multiple fields to address specific challenges. Convergence builds on fundamental progress made within individual disciplines AND cuts across disciplinary boundaries in these fields.

While Convergence and interdisciplinary research are closely allied, Convergence is different because it goes beyond collaboration: Convergence is the integration of historically distinct disciplines and technologies into a unified whole that creates fundamentally new opportunities for life science and medical practice.

Convergence signifies a broad rethinking of how scientific research can be conducted in order to capitalize on a range of knowledge bases, from microbiology to computer science to engineering and design. In other words, the Convergence Revolution does not rest on a particular scientific advance but on a new integrated approach for achieving advances.

Convergence is 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.

This report is based on workshops, interviews with experts, and reports from science, technology, academia, nonprofit organizations, government, and industry.

It includes:
(1) an overview and history of the Convergence revolution in biomedicine and healthcare;
(2) a brief discussion of major advances and governmental, academic, and industrial progress since the publication of the 2011 MIT Convergence report, *The Third Revolution*;
(3) an overview of health care trends and costs demonstrating an urgent need for Convergence solutions;
(4) case studies of three disease-specific challenges and examples of how Convergence is helping to solve them;
(5) case studies of four exciting Convergence technologies impacting multiple disease states;
(6) an overview of Convergence progress and challenges specific to industry, education, government, and funding; and
(7) recommendations for accelerating the Convergence revolution.
Overview Of The Convergence Revolution

History

Convergence represents the Third Revolution in life sciences. Revolutions in science have always involved a synthesis of new ideas, methods and disciplines. In 1895, the x-ray led to a revolution in imaging that was followed by the electrocardiograph in the early 1900s. The electrocardiograph, in time, led to modern computerized axial tomography (CAT) scans and magnetic resonance imaging (MRI) scanners.

By the 1950s, Max Delbruck and Salvatore Luria had brought particle physics concepts to build the field of molecular biology. In 1953, new x-ray diffraction techniques allowed James Watson, Francis Crick and Rosalind Franklin to discover the structure of DNA, which supported molecular and cell biology. Discoveries of proteins and other driving forces in the cell made it possible for researchers to probe inner workings of diseased cells in order to better understand cancer and other illnesses and, later, to modify cellular processes through genetic engineering and biotechnology.

In the 1970s, the National Cancer Institute (NCI) funded basic science centers organized around molecular and cell biology approaches for cancer research. By the 1980s, university-trained scientists had joined biotechnology companies such as Genentech, Biogen and Amgen, which developed new treatments for cancer, multiple sclerosis, and hepatitis. These companies and others established a new biotechnology economic sector and created tens of thousands of jobs.

In the 1990s, the National Institutes of Health (NIH) and the Department of Energy (DOE) funded genetics and supercomputing research, which helped lead to a “Genomics Revolution.” Researchers began to identify genetic foundations of many diseases and to develop new treatments based on each patient’s unique genetic makeup and disease subtype. Their goals were to reduce reliance on costly, ineffective medications and ease their side effects. In the early 2000s, an NCI alliance founded small ($2 million-$3 million) research centers, building communities of researchers from different disciplines—engineering, material science, chemistry, mathematics, physics, information, and life sciences—in order to solve pressing health problems.

All of the above developments involved combining concepts and technologies from multiple fields. These “crossovers” have begun to scale up. Today, we are reaping the early benefits of a Convergence Revolution in which the tools, methods, concepts, and processes of engineering (including physical and computer science engineering) are increasingly used in biological research. Conversely, life scientists’ deeper understanding of complex evolutionary systems influences physical science and engineering.

Recent developments

As a result of the Convergence Revolution, biomedicine has seen major developments in fields such as imaging, biomaterials, nanotechnology, and cellular engineering. Recent breakthroughs include: a brain-implanted computer chip allowing a previously paralyzed patient to move his arm; a retinal prosthesis to help restore sight; and biologically derived molecules (proteins, antibodies, vaccines and cells) for treating anemia, heart attacks, and stroke, or inhibiting cancer growth.2, 3, 4 (Many other biomedical examples are described in Chapter 2.)

While this report focuses on the impact of Convergence on biomedicine and human health, it is important to note that the Convergence Revolution has led to important developments outside of biomedicine.

In agriculture, the tools of synthetic biology are now being used to tailor food products to meet specialized dietary needs, to reduce insecticide use, and to surmount drought and other difficult growing conditions. In the energy arena, researchers and companies are finding ways to harness the potential of microorganisms and plants to produce
Today, we are reaping the early benefits of a Convergence Revolution in which the tools, methods, concepts, and processes of engineering (including physical and computer science engineering) are increasingly used in biological research.

fuels. To protect the environment, scientists are developing biodegradable plastics made from renewable biomass and biosensors to monitor environmental changes. They are also using microorganisms and their constituents to detoxify industrial waste. In the growing field of “machine” or “deep” learning, scientists are employing new models of the brain and neural networks to “train” computers to solve complex problems ranging from image recognition to financial prediction.

The Convergence Revolution holds the potential to address the most significant challenges of human existence in the 21st century.

Recent Initiatives

Government

The White House and federal agencies have launched a variety of programs to spur education, research and development across many fields of science. In 2012, the White House cited the importance of Convergence in a National Bioeconomy Blueprint, outlining steps agencies would take to drive economic activity powered by research and innovation in bioscience. The White House and supporting agencies have since launched:

• The BRAIN Initiative (Brain Research through Advancing Innovative Neurotechnologies), a major public-private partnership to accelerate the development and application of innovative technologies aimed at understanding how individual cells and complex neural circuits interact in order to find new ways to treat, cure, and prevent brain disorders. As of 2015, some $200 million has been committed by the federal government, along with $240 million by foundations and private research institutions, and $30 million by corporations. An additional 2016 federal investment of $85 million will be divided among the NIH, DARPA, NSF, the Food and Drug Administration (FDA), and Intelligence Advanced Research Projects Activity.

• The Precision Medicine Initiative calls on a Convergence model that uses Big Data and analytics to advance medical treatment, drawing on a deep understanding of human biology. The initiative, announced in 2015 with a $215 million investment in the 2016 budget, aims to create a million-person cohort to collect and analyze genetic, environmental, and other medical data for comparison across the largest patient database ever created. Funds are divided among the NIH ($200 million), FDA ($10 million), and the Office of the National Coordinator for Health Information Technology ($5 million).

• A $1 billion National Cancer Moonshot Initiative was launched in 2016 to accelerate research to develop cancer vaccines, early detection methods, immune and other therapies, genomic analysis of tumor and surrounding cells, and enhanced mechanisms for data sharing. Most of this initiative will involve Convergence tools and technologies.

In addition, the Defense Advanced Research Projects Agency (DARPA) has formed a Convergence-oriented Biological Technology Office (BTO), which has a research portfolio that includes fabrication, neuroscience and infectious disease. Among other projects, BTO-funded researchers are working on prosthetics to restore soldiers’ lost limbs and sensation; microphysiologic systems (human “organs on a chip”) to diminish the need to use animals in drug testing; and new ways of programming or engineering bacteria to produce novel therapies (or valuable chemicals for use as alternative fuels). DARPA has also funded nanotechnology research aimed, for example, at treating traumatic brain injuries and related infections, and is pursuing the use of synthetic biology to re-engineer human cells to resist disease.
A nanotechnology alliance formed in 2004 by the National Cancer Institute (NCI) has led to the formation of more than 85 companies (many founded by academic researchers) and to 17 clinical trials. With additional financing from industry, foundations and other agencies, including the FDA and National Institute of Standards and Technology (NIST). Alliance scientists around the country are working on nanoparticles to deliver anti-cancer drugs directly to tumor cells; biosensor chips to speed drug development; and a handheld cancer detection device that combines imaging, magnetic nanoparticles, and a smartphone.

The NCI Clinical Proteomics Tumor Analysis Consortium (CPTAC), an investment of $150 million since 2006, converges the “omics” sciences by extending The Cancer Genome Atlas genomic and transcriptomic characterization with concurrent proteomic characterization of nearly 400 samples. By working with FDA and NIST, the datasets released have already been used to develop multiplexed assays. The expansion of CPTAC in FY2016 will support additional tumor type characterization and Convergence Big Data centers to analyze more than 2,000 proteogenomic samples from domestic and international partners. More importantly, they will fund proteogenomic translation centers that are linked to NCI-sponsored trials so that Convergence science will be tested in a more real-world setting.

The National Science Foundation (NSF) has funded Convergence research on tissue and cellular engineering, computational neuroscience and an artificial retina that is now on the market. With NCI, NSF has offered workshops on 3D printing for biological tissue, advanced manufacturing, and immune therapeutics.

In May 2016, NSF Director France Córdova announced more Convergence research as one of nine “big ideas” for the future of NSF. NSF aims to “strategically support research projects and programs which are motivated by intellectual opportunities and/or important societal problems, and which would benefit from the Convergence of (subsets) of physical sciences, biological sciences, computing, engineering, and the social and behavior sciences.”

In the educational arena, the White House initiated a public/private program aimed at strengthening educational efforts in science, technology, engineering and mathematics (STEM) fields from kindergarten through higher education. NSF and other agencies have funded STEM education and teacher development for primary, secondary, and post-secondary schools. While not Convergence itself, STEM education is the required foundation for individuals who will have the intellectual alacrity to cross fields. NSF also funds university programs bringing together different scientific disciplines and diverse communities of faculty and students, often on the same campus. And with four- to-fivefold increases in grant funding to engineering and bioengineering departments between 2000 and 2014, NIH’s National Institute of Biomedical Engineering and other institutes have raised the funding of engineers and bioengineers in biomedicine from about $104 million to about $450 million in fourteen years. While this is progress, these represent relatively small investments in research conducted primarily in engineering and bioengineering departments, at less than 2 percent of the total NIH research funding in 2014.
Academia

In recent years, many universities have launched or expanded Convergence efforts, including the following:

- At Harvard University, the Wyss Institute for Biologically Inspired Engineering crosses disciplinary and institutional lines to engage in “high-risk” research aimed at developing innovative engineering solutions, commercial products and therapies in multiple fields. The Harvard School of Engineering & Applied Sciences has no departments and operates as a single faculty across a wide spectrum of disciplines in both teaching and research activities.

- The Georgia Institute of Technology (Georgia Tech) has in recent years formed a number of Interdisciplinary Research Institutes based on Convergence. The first of these was the Parker H. Petit Institute for Bioengineering and Bioscience (IBB), established in 1995, bringing together biochemistry, biology, and the various disciplines of engineering. IBB today has more than 170 faculty members and is home to 17 research centers, each based on the concept of Convergence.

- Carnegie Mellon University offers interdepartmental learning and collaboration in engineering, science, information technology and medicine; training in the neural basis of cognition; and information science for medical scientists. Its College of Engineering offers PhDs in machine learning and computational biology and, with the University of Pittsburgh, engineering training for medical scientists.

- The University of Texas at Austin has created an Institute for Computational Engineering and Sciences (ICES). This multidisciplinary research unit and graduate program advances computational science and engineering in engineering, science, and medical problems; it functions independently of department, reporting directly to the Vice President for Research.

- The University of Connecticut has established the Raymond and Beverly Sackler Center for Biomedical, Biological, Physical and Engineering Sciences to focus on cutting edge research in the area of regenerative engineering to regenerate complex tissues and organ systems.

- The University of Chicago’s new Institute for Molecular Engineering offers a problem-based approach to research in areas such as synthetic polymers, immunoengineering and cancer therapeutics, quantum materials, and information technology.

- The University of Illinois at Urbana-Champaign is in the process of founding a medical school that will incorporate principles of engineering, technology, and Big Data into its educational program—with an ultimate goal of providing better health care to more people at lower costs.

- The California Institute of Technology (Caltech) offers fellowships allowing undergraduates to learn techniques and approaches in two or more laboratories. Graduate students may have advisors and faculty mentors from various scientific fields or cross-disciplinary centers.

- Tufts University’s Institute for Innovation aims to address and solve some of the world’s most pernicious and important problems in human health, by creating networks, assembling teams, and focusing early and often on market needs. In 2016, the Allen Discovery Center at Tufts was established with an emphasis on Reading and Writing the Morphogenetic Code. The overall goal of this Center is to create new, interdisciplinary approaches to the understanding and control of morphogenetic information—the mechanisms and information by which biological systems control anatomy from the level of tissues to the entire body plan.

Of course, many other colleges and universities also offer Convergence education and research opportunities, but often without the support needed to thrive.
Industry

The biomedical industries are often divided into pharmaceutical, biotechnology, device and diagnostic segments, and have been profoundly affected by the Convergence Revolution. The advent of Big Data in biomedicine—along with new methods, tools and equipment for imaging, modeling, genomic analysis, nanotechnology, bioengineering and regenerative medicine (among other breakthroughs described in Chapters 2 and 3)—has led to the formation of many new companies and the transformation of existing ones. Examples include:

- Verily (formerly Google Life Sciences) is developing and employing Convergence technologies to “map” the healthy human body. Some goals of Verily’s “baseline study” are to predict the onset of diseases far earlier than is currently possible; to develop individualized treatments based on biological, genetic, behavioral, and environmental data; and to identify biomarkers that indicate whether individuals are more or less susceptible to various diseases. Verily’s research and development program originated with a Google-designed contact lens for diabetics that continuously monitors glucose in tears.¹⁹

- Computer and software companies such as Apple, IBM, and Microsoft now offer Convergence innovations that combine information science, imaging and sensors to: track and monitor health, fitness and disease; help health care systems, hospitals, and insurance companies cut costs; and gather in-depth, long-term data about participants in clinical trials.²⁰

- A small company called Welldoc is commercializing a mobile app that analyzes diabetes data entered by the patient, including blood glucose and medications.²¹

- With nanotechnology developed at the California Institute of Technology, Cerulean Pharma is developing a nanoparticle drug delivery platform that can squeeze through new tumor blood vessels and help make cancer chemotherapy safer. Currently in early and mid-stage clinical trials, their lead nanoparticle drug treats a variety of cancers in combination with Avastin and paclitaxel.²²

- In the diagnostics arena, a Cambridge-based nonprofit company called Diagnostics for All is developing a low-cost, paper-based platform to diagnose disease in the developing world.²³

Associations and Foundations

Since the 2011 MIT report, Third Revolution: Convergence of the Life Sciences, Physical Sciences and Engineering,²⁴ was issued, important documents focusing on Convergence have been published by the American Association for the Advancement of Science, the National Academy of Sciences, and other authorities.²⁵ Numerous organizations, such as the Kavli,²⁶ Bill and Melinda Gates, Raymond and Beverly Sackler Foundations²⁷ and the Burroughs Wellcome Fund,²⁸ among others, have generously supported Convergence initiatives, institutes, prizes, awards, and centers.

In sum, government, university, philanthropy, and industry efforts are using Convergence approaches to better understand wellness and disease, develop new treatments and prevention, and provide greater access to health care.

But much more could be done to accelerate the impact of Convergence on new approaches to health and healthcare.
As described in Chapter 4:

- While the U.S. remains the world’s largest funder of research and development, government funding for medical research has not kept pace with increasing rates of disease and economic inflation.29, 30 Despite recent efforts, funding is not adequately geared toward Convergence approaches or inclusive enough of researchers outside the life sciences. Meanwhile, other nations—especially in Asia—are increasing their global share of spending for science and engineering education, for research and development, and for Convergence-related facilities.

- Current university structures organized around disciplinary departments do not readily lend to Convergence education or research, because incentives for professional advancement reward individuals working in disciplinary siloes, rather than those who collaborate deeply with colleagues.31

- The dominant business model of the biopharma sector still depends on “blockbuster drugs,” which can be at odds with some Convergence approaches.

If these challenges are not overcome, the burdens of disease will increase exponentially and the U.S. lead in science and engineering internationally will diminish—at tremendous individual and societal costs.

Healthcare: Humanitarian and Fiscal Costs

United States

More than 2.5 million people die in the U.S. each year, primarily due to ten diseases: heart disease, cancer, chronic lower respiratory disease, accidents (unintentional injuries), stroke (cerebrovascular diseases), Alzheimer’s disease, diabetes, influenza and pneumonia, kidney disorders, and depression-driven suicide. Chronic conditions such as heart disease, stroke, cancer, and diabetes are among the most costly of all health problems.32 As of 2012, approximately 117 million people—nearly half of all adults in the U.S.—had at least one chronic health condition, and one of four adults had two or more.33 Chronic conditions cause 70 percent of deaths each year in the U.S., and account for 86 percent of American health care treatment costs.34

In 2014, national health expenditures reached $3 trillion, or $9,523 per person, and accounted for 17.5 percent of the Gross Domestic Product (GDP).35 As the U.S. population ages, health spending is projected to grow at an average rate of 5.8 percent per year (1.1 percent faster than the GDP). The health share of GDP is expected to rise from 17.4 percent in 2013 to 19.6 percent by 2024.

Cost control is critical and it will depend to a large degree on innovation. Convergence—and the corresponding transformation of healthcare it can drive—is key to innovating our way out of these increasingly burdensome healthcare costs. Without significant breakthroughs in early lower-cost diagnosis, prevention through lifestyle changes, and novel treatments—precisely what the Convergence Revolution offers—these healthcare fiscal trends will undermine our national competitiveness.
Global

Internationally, heart disease, stroke, lower respiratory infections and chronic obstructive lung disease have remained the top killers during the past decade; cancer, which is often underreported, is also high on the list. HIV deaths decreased slightly, from 1.7 million deaths in 2000 to 1.5 million in 2012. As in the U.S., chronic diseases caused increasing numbers of deaths worldwide, with lung, tracheal and bronchus cancers causing 1.6 million deaths in 2012, up from 1.2 million deaths in 2000. Similarly, diabetes is on the rise internationally, causing 1.5 million deaths in 2012, up from one million deaths in 2000. Common diseases like influenza lead to significant loss of productivity. Emergent diseases like the Ebola and Zika viruses, along with the possibility of bioterrorism, are of great concern.

All-in-all, there is clearly a need for new approaches. Growing populations; soldiers beset by brain injury, post traumatic stress disorder and other disabilities; new bacterial and viral illnesses; the scourges of auto-immune, chronic and emergent diseases; and increases in risky health behaviors such as smoking and poor dietary habits all demand innovative research to find better solutions.

Such approaches must lead to better understanding of disease mechanisms and of the interactions among genetics, cells, organs, and the environment. We need new methods to prevent, diagnose, treat, and cure disease, and to increase understanding of “wellness” and how to achieve and maintain it. Progress will require the joint efforts of scientists, engineers, educators, funders, companies, and governments, along with new approaches to education and labor force development.

Chapter 2 outlines three major disease areas and promising Convergence approaches. Chapter 3 describes four exciting new technology areas and how they are impacting disease.
Endnotes


4 A.C. Ho et al., “Long-Term Results from an Epiretinal Prosthesis to Restore Sight to the Blind,” *Ophthalmology* 122 (8), 1547–54 (2015).


14 National Cancer Institute, Clinical Proteomic Tumor Analysis Consortium.


Federation of American Societies for Experimental Biology, NIH Research Funding Trends (2016).


Centers for Disease Control, Chronic Diseases: The Leading Causes of Death and Disability in the United States (2016).

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World Health Organization, The top 10 causes of death, Fact Sheet Number 310 (2014).
Infectious diseases such as Ebola, Zika, and malaria still ravage human populations. The tidal wave of chronic diseases—diabetes, heart disease, cancer—continues unchecked. Aging populations everywhere fear and suffer from dementia and other brain disorders. These and other unmet health needs could benefit from Convergence research efforts that bring powerful new technologies and promising new therapeutic opportunities. This chapter briefly surveys a number of examples that illustrate opportunities for major—sometimes revolutionary—progress in improving human health.

**Brain Disorders**

**Introduction**

The human brain is the least understood major organ in our body. Moreover, brain disorders such as depression are widespread and often co-exist with other chronic diseases. When the brain malfunctions in neuropsychiatric disorders such as schizophrenia, or loses its capacity in dementias, the consequences can fundamentally change who we are. And the brain, consciously or not, dictates our behaviors—including those that undermine our wellbeing and thus contribute to illness.

To radically improve our understanding of the brain, we will need Convergence approaches for (1) engineering new diagnostic approaches and non-invasive therapies; (2) developing new nanotechnology carriers to get medicines and novel genetic therapies into the brain; (3) developing tools to quantify behaviors that can be used for both diagnosis and behavioral modification; and (4) exploring unexpected connections between the brain and other organs such as the heart and gut.

**Convergence Solutions**

Research on the brain is poised to accelerate. Promising innovations in brain science span many different areas of research, including:

- **The developing brain** changes in response to early experience. In some cases, when things go wrong, early intervention can help rewire the brain and provide better outcomes. But early diagnosis has been challenging, since many parents are unaware of signs of disease or unable to pay for evaluation by specialists. In response, researchers at Duke University have come up with a novel screening approach for autism that combines engineering and medicine. They developed a computer vision system that tracks eye movements of a child watching a video and a scoring algorithm that identifies children at risk by documenting whether their eyes track movement poorly. They worked with Apple to create an iPhone-based app. With parental consent, the app monitors a young child’s face as he or she watches a video. The video is analyzed by the scoring algorithm, which then advises the parents if they should consult a specialist for further analysis.

In another early diagnostic approach, researchers at the University of California, San Diego and the University of Illinois at Urbana-Champaign have developed a system to use cardiac signals to identify infants at risk of cognitive impairments. The system presents auditory or visual signals to the baby, and measures variability in how hard the heart is working, as a proxy for the function of the prefrontal part of the brain. The aim is to use advanced statistical methods to non-invasively predict developmental delay as early as six months of age.
The scientists hope that pediatricians will eventually include routine use of these and other screening tools to measure brain health as well as weight gain and other standard well-baby metrics, so that at-risk children can get help early. More broadly, these examples are part of a broader Convergence effort to quantify behaviors that are relevant to health enabled by engineers, developmental biologists, and clinicians working together.

• **As the population ages**, the incidence of debilitating brain disorders such as Alzheimer’s and Parkinson’s diseases will increase significantly. More fundamental research is needed to understand the basic biology of the degenerative disease processes to develop more effective therapeutic approaches. Such efforts have been helped by a new method that enables scientists to see deep into brains and to build more detailed 3D maps of neural circuits. A powerful technique called **optogenetics** adds a light-sensitive protein to specific neurons in animal models, enabling those neurons to be turned on and off with a flickering light. Scientists at MIT have identified brain cells that store a particular memory; the researchers are exploring stimulation techniques that might one day recover memories lost to Alzheimer’s disease, or halt degenerative processes.

New evidence suggests that adult brains are more plastic and adaptive than once believed. Researchers at the NIH have used sophisticated technology to produce an oscillating magnetic field that stimulates a small electrical current in specific parts of the brain. When, in parallel with this non-invasive stimulation, a patient also performs brain-training tasks on a computer, cognitive improvements such as gains in short-term memory have been observed. The scientific work underlying this advance required not only neuroscience expertise, but also advanced imaging tools and novel technologies for stimulating specific parts of the brain.

• **Traumatic brain injury** is an increasingly recognized public health problem. Convergence approaches suggest new strategies to repair these injuries and restore brain function. Researchers at MIT and Massachusetts General Hospital are using high-resolution imaging such as MRI and diffusion tracer imaging to locate injuries and identify which specific neural circuits are damaged.

In another example, anesthesia—the induced coma that shields surgical patients from pain—can cause unwelcome changes in the brains of older patients. Targeted brain stimulation techniques might one day enable doctors to wake people from anesthesia more quickly, shortening their unconscious period. Clinical trials to test this strategy are already underway.

• **Neuropsychiatric disorders** are currently diagnosed based only on a patient’s overt symptoms because there are no known brain biomarkers for these diseases. Without biomarkers we cannot, at present, predict risk or time of onset. However, researchers at the Broad Institute of MIT and Harvard, with global collaborators, have used massive genomic sequencing techniques, sophisticated data processing, and cutting-edge experimental work in mice to identify subtle genetic differences in people with schizophrenia. They have found mutations that correlate with malfunctioning brain development processes. This work lays critical groundwork for discovering biomarkers and developing early diagnostic tools and therapies. Other work on these diseases examines brain function at the level of specific neural circuits and individual neurons. Technologies now under development measure the voltage dynamics in a single neuron and correlate complex signals to behaviors. The goal is to predict neuropsychiatric illness before symptoms appear, to predict behaviors caused by these disorders, and to devise therapeutic interventions.
Summary

The brain presents an astonishingly large and complex set of neural circuits that gives rise to consciousness, as well as to the capacity for emotions such as empathy and grief. Greater ability to analyze neural circuits and circuit failures will be important in understanding brain disorders. Electrical engineering and systems analysis would bring useful skills, perspectives, and technology to this endeavor. A purely biological approach may not be sufficient—Convergence is necessary. New technologies for non-invasive brain stimulation depend on sophisticated electromagnetic tools. Extraordinarily sensitive physical methods to monitor electrical activity in complex neural circuits, in conjunction with new high throughput sequencing methods—including mapping which genes are active in which cells in both normal brains and those with disorders—will provide high resolution insights into the neurobiology of the brain in health and disease.

IT-based sensors, smart devices, and sophisticated software apps are needed to quantify behavior, both for basic research and for early screening for brain disorders, and perhaps ultimately for therapy—Fitbits for the brain, perhaps. When paired with new engineering approaches that allow researchers to see deeply into the brain and locate specific memories or behaviors, the potential for rapid progress on understanding and alleviating brain disorders becomes clear. Clearly cross-functional research teams and Convergence approaches can accelerate that progress.

Infection and Immunity

Introduction

Recent outbreaks of Ebola in Africa and Zika in the Americas have focused public attention on the threat from infectious disease. These are both viral diseases, for which antibiotics do not work and for which no FDA-approved vaccines exist. Nor are there approved vaccines for a number of other deadly viral diseases including dengue fever and HIV/AIDS. Potentially even more harmful, however, is the increasing spread of antibiotic resistance to the drugs used to treat familiar bacterial infections such as tuberculosis, strep throat, and staph infections. Drug-resistant bacteria infect at least two million people in the U.S. every year, and resistance to the two “last resort” antibiotics is spreading, especially in hospitals. At present there are very limited treatment options for extensively-multi-drug resistant tuberculosis. New antibiotics are badly needed, but this is a race that cannot be won through conventional drug development alone. The more widely a drug is used, the more quickly bacteria will evolve to acquire a resistance to it.

Convergence Solutions

Fortunately, new approaches are emerging that bring together immunology, engineering, chemistry, and the powerful new molecular genetic tools of synthetic biology. These Convergence approaches have the potential to create fundamentally new ways to combat infection and strengthen immunity. Examples include:

- **Eliminating mosquitoes.** The technique of releasing large numbers of sterile male insects has been successfully used to largely eliminate screwworm infections that cause havoc in U.S. livestock herds. Trials of a related approach—releasing mosquitoes infected with a bacterium that makes them resistant to viral infections such as dengue—are underway in China and Brazil. A more sophisticated version of this strategy is now being developed by researchers at Harvard, using the new technology of synthetic biology to rewire the genetics of mosquitoes to breed healthy females who always pass on a fatal gene to their offspring. Released in large quantities, the mutation spreads through entire populations by an engineered approach known as a gene drive, potentially largely eliminating the vectors for Zika, dengue, and perhaps even malaria.
Cancer immunotherapy. A number of recently approved new drugs block the signals cancer cells use to inactivate the body’s immune system. Known as *immune checkpoint inhibitors*, these drugs enable the body’s own T-cells to find and kill tumor cells. Immunotherapy represents an unprecedented breakthrough in cancer therapy; at present, this revolutionary approach does not work in all patients or for all types of cancer—least, not yet. More research is needed to fully understand its mechanisms, but the general strategy is clear: to rewire the immune system’s signaling networks in the appropriate way for each patient to effectively activate a patient’s immune cells against their cancer. To do so requires a detailed understanding of the molecular variants represented in an individual’s cancer.

A key enabling technique for this strategy is *single-cell mass cytometry*, developed by Stanford University scientists, which labels antibodies that probe the multifactorial characteristics of individual cells with distinctive heavy metal ions. As many as 50 different antibodies can be used simultaneously to generate large amounts of data that require sophisticated computational analysis.

Creating new vaccines. Vaccines have saved more lives than any other therapeutic approach. Now novel convergence strategies can help develop new ones. The long and so far unsuccessful effort to develop an HIV vaccine illustrates one way viruses evade immune surveillance: the virus mutates rapidly, changing the molecular sites that a vaccine targets. One strategy is to take advantage of the virus’s rapid mutation: researchers make a molecular map of the potential ways the virus can evolve. They then design complex vaccines that encourage mutations that undermine the virus’s ability to survive.

Another approach is to boost the potency of vaccines, without harming the patient. For example, a vaccine comprised of a killed or disabled virus—like the flu vaccine—could be risky for more serious diseases or in immune-compromised individuals. A safer alternative is to use fragments of a protein produced by a disease-causing virus or bacterium. This strategy has worked for hepatitis and diphtheria, but not for many other diseases, where the immune response is either too weak, or causes unwanted side effects. One strategy to work around these problems delivers a protein fragment vaccine directly to the lymph nodes, where immune cells are concentrated. Chemical engineers at the Koch Institute at MIT developed a vaccine with a fatty tail and attached it to albumin, a molecule found in the blood that binds to fatty molecules and transports them to the lymph nodes. In effect, the vaccine hitchhikes on albumin to the lymph node, minimizing side effects in other parts of the body. Vaccines targeting HIV, cervical cancer, and melanoma (a deadly skin cancer) in mice generated large number of T-cells specific to the viral or tumor protein. The elicited immune response was as much as 10 times stronger than for the protein fragment alone, and strong enough to slow tumor growth or even shrink tumors. The researchers are moving this novel vaccine strategy toward clinical trials. (See also the section on Cancer on page 33.)

Rewiring genetic circuits to protect against disease. Even more powerful methods of defeating infections and boosting the body’s immune system may come from synthetic biology strategies that engineer new genetic circuits in living cells or in cell-free extracts on paper sensors.

Researchers at Harvard and MIT are creating engineering circuits in bacteria that live in the human gut. The new circuits have a sensor function that can identify the presence of a pathogen and a trigger function that then switches a memory function from one state to another. In mice treated with an antibiotic (the “pathogen” for the experiment), the recovered bacteria had not only survived several generations with their synthetic circuitry intact, but had successfully switched their memory states. In principle, this technique could be used to create synthetic probiotics that would identify the presence of dangerous
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bacteria in the gut, acting as living diagnostics and, potentially, providing therapies.

These tools provide, in principle, the ability for synthetic genetic circuits to sense the status of a living cell and use that information to modify its activity—initiating or shutting off production of a protein, for example. Critical to this approach is an ability to switch specific genes on and off, with synthetic regulatory mechanisms that are easily designed, compatible with living tissue, and not easily disrupted by other biological processes. A class of regulatory mechanisms called "toehold switches" can be inserted into a cell's existing DNA and activate genes in response to a custom-designed RNA signal.\textsuperscript{57} To illustrate the potential power and flexibility of this approach, a team of scientists from Harvard and Boston University inserted 12 different switches—each controlling a different cell function—into a single cell, and demonstrated that each functioned as planned.\textsuperscript{58} Toe-hold switches, added to the growing set of synthetic biology tools, can monitor RNA in living cells and advance basic understanding of living systems.

Synthetic biology tools also promise the rapid development of low-cost diagnostics for emerging pathogens or orphan diseases, and real-time monitoring for a range of medical conditions. For example, MIT and Harvard scientists have figured out how to export engineered biological circuits outside living cells. Cellular material is freeze-dried on paper or other substrates, where they remain stable at room temperature until they are re-activated by adding water.\textsuperscript{59} Such paper-based diagnostic strips are easier to use than antibody-based diagnostics and can detect both antibiotic-resistant pathogens and other disease agents. In one demonstration, more than 20 different sensors for Ebola that changed color when the virus was present were developed in less than a single day—ideal for field use.

Summary
New high-throughput methods of probing the properties of living cells combined with advanced computational tools are on track to enable personalized immunotherapies against cancer. Clever chemical strategies to package powerful vaccines so that they greatly strengthen the body's immune systems to combat disease while avoiding most side effects are already showing great promise. Convergence strategies such as synthetic biology are rapidly transforming the means of identifying and treating infections, and opening up fundamentally new ways to monitor and modify the properties of living cells. These approaches could eliminate disease vectors, enlist modified gut bacteria as living sensors against disease, and allow a rapid response to new epidemics with simple paper-based, field-ready diagnostics. But we still need a deeper understanding of the immune system and the signaling networks that control it, as well as further development and testing of synthetic biological circuits to do so. In addition to the clinical promise, these Convergence strategies also are powerful experimental tools to understand fundamental principles of living organisms.

Cancer
Introduction
Over the last 25 years, cancer death rates in the U.S. have decreased. Yet an estimated 1.7 million new cases will be diagnosed this year and almost 600,000 people will die from cancer—so the battle is far from over.\textsuperscript{60} Investments in basic research have laid a foundation of knowledge, especially the molecular and cellular mechanisms involved in cancer and the interplay among genetic and environmental causal factors. Dozens of new cancer drugs have been developed and commercialized, and radiation therapy has gotten more precise. Yet chemotherapy and radiation are still the dominant modes of treatment, and they often fail in managing cancer long-term. Tumor resistance to chemotherapy, inefficient delivery of drugs to the target site, and metastatic spread to
distant organs, make cancer very difficult to control and cure. In addition, many treatments have long-term side effects. With an aging population, cancer rates and costs will climb in coming decades.

To make a significant difference, fundamentally new approaches are needed, including Convergence strategies that bring insights from fields as diverse as nanotechnology, immunology, and advanced engineering. These include:

• New, inexpensive, and minimally-invasive methods for early detection, when treatment is easier or surgery is a viable curative option;

• Combination therapies and engineered nanoparticle systems to deliver them in a concentrated form without damaging surrounding cells;

• Re-programming and stimulating the human immune system so that it can recognize and kill cancer cells; and

• Personalized treatments, using human genomic technologies and new animal models to pre-test the effectiveness of cancer drugs.

Convergence solutions
Recent innovations that show exceptional promise include:

• Early Detection Via Urine Test. If tumors are detected at an early stage in their development—before they have metastasized or grown to a size that perturbs normal organ function—they can be readily removed surgically. Scientists at the Koch Institute at MIT have developed a urine test based on synthetic biomarkers that can be detected using paper strips similar to home pregnancy tests. The synthetic biomarkers are engineered into nanoparticles that also contain materials that interact with specific proteins. When the nanoparticles are injected into a patient, they target the tumor and interact with it in a way that releases the synthetic biomarkers, which then pass into the patient’s urine. The treated paper strips, known as lateral flow assays, react with the biomarkers to give a quantitative measurement of their, and the cancer’s, presence.

This synthetic biomarker technique can detect colorectal cancer as well as other diseases such as liver fibrosis and thrombosis, a common disease of blood clotting, in animal experiments. It is now under development for human trials. The method can potentially be tailored for a wide variety of non-infectious chronic diseases, including many cancers. It is simple and inexpensive enough to be used as a point-of-care diagnostic at home, in a doctor’s office, or even in low-resource settings.

• Early Detection Via Blood Test. Cancers often shed tumor fragments, such as DNA or other nucleic acids, that then make their way into the bloodstream. That raises the potential of using a blood sample as a kind of “liquid biopsy.” Since cancer DNA contains mutations that can, in principle, be detected by sequencing, much effort is being put into developing rapid, cost-effective, and highly sensitive sequencing techniques. For example, a new sequencing method devised by scientists at Stanford was able to detect blood-born tumor DNA from most patients with lung, colorectal, and a number of other cancers. Scientists at Johns Hopkins University, where the idea originated, report that the method can detect cancer long before symptoms arise. However, while the technique is quite specific (with few “false positive” signs of cancers), it does not work in all patients, for reasons that are not yet understood. Nor is the cost of sequencing yet low enough.
that it could become a screening tool for use with annual checkups. But work is proceeding, and the technique is being commercialized. Similar Convergence approaches are being developed to exploit circulating exosomes and tumor cells as diagnostics, with some already in clinical use.

• Combination Therapies. Nanotechnology is also being used to combat cancer by delivering multiple drugs or other therapies simultaneously, with the aim of overcoming tumor drug resistance. Other therapies can include proteins and genetic material. For example, scientists at Northwestern University developed gold nanoparticles that can reach the brain; they contain segments of RNA molecules that could penetrate brain tumors and turn off or silence genes, effectively stopping the tumors from growing.66 (See also the Nanotechnology section in chapter 3.)

Another example is the use of “smart” nanoparticles to deliver two or more therapies in a controlled sequence. Scientists at MIT’s Koch Institute have included two different chemotherapy drugs in a multi-layered nanoparticle. The first drug weakened lung or breast tumors by shutting down a growth pathway, and the second drug, released hours later, targeted the tumor DNA.67 Engineering this package required a nanoparticle with a spherical inner droplet (containing the second drug) surrounded by a fatty outer shell (containing the first drug). The nanoparticle was then coated with a polymer to protect it from the body’s waste removal systems, and tagged with a substance that directs it to tumor cells. The resulting one-two punch to the tumor was far more effective in animal models than conventional chemotherapy, and was especially effective against a very aggressive type of breast cancer that tends to strike younger women.

• Cancer Immunotherapy. The immune system is adept at attacking foreign invaders, but often fails to recognize and kill tumors because they arise from the body’s own cells. But recruiting or training the immune system to recognize and attack cancer cells would be far more advantageous than relying on external agents such as toxic drugs or radiation. One approach is removing T-cells—one component of the immune system—from a patient and re-programming them to recognize and attack tumor cells. Another approach is to attack tumors with antibodies, activating another part of the immune system. Scientists at the Koch Institute at MIT recently discovered a way to activate both parts of the immune system simultaneously by fusing a signaling molecule to part of an antibody molecule.68 In animal tests this approach also activated T-cells. Adding re-programmed T-cells to the therapy package in a mouse model of an aggressive form of melanoma resulted in the complete disappearance of tumors in most of the mice. Even months later, the mouse immune system destroyed re-injected cells. This approach illustrates the potential for immunotherapy to treat recurrent cancer.

Another approach is to develop cancer vaccines that can prepare immune cells to recognize a particular cancer in advance. Scientists are engineering a new class of cancer vaccines that evoke a potent T-cell response against tumors. But to be effective, the vaccine must reach the body’s lymph nodes, where large populations of immune cells reside. So the scientists engineered the vaccines to latch onto the protein albumin, which is found in the bloodstream, and which both shields the vaccine from the body’s waste removal systems and transports it to the lymph nodes.69 This novel immunization strategy in animal experiments elicited a very strong immune response in the form of large numbers of vaccine-specific T-cells in the bloodstream. This approach is now under development for a vaccine against lung cancer. (See also the Infection and Immunity section on page 31.)

Still another immunotherapy approach exploits the ability of T-cells to penetrate tumors and reach target sites that nanoparticle therapeutics cannot typically reach. Life
scientists and engineers at the Koch Institute at MIT were able to connect engineered nanoparticles containing chemotherapy drugs to the surface of T-cells. When the engineered T-cells were reintroduced into mice with lymphatic tumors, the T-cells traveled to target sites and released the therapeutic payload, enhancing survival rates.

- **Accelerated Drug Testing.** Drug screening in animal models of cancer is typically limited to a few drugs per animal, making the screening of numerous drugs, in combinations or alone, expensive and time-consuming. Teams of engineers and cancer specialists at MIT and the University of Washington/Fred Hutchinson Cancer Center have developed microdevices that can be implanted into tumors, where they release tiny doses of drugs into different regions of the tumor. The devices can screen many drugs within a single animal. The observed responses to the micro-injected drugs accurately predict responses to the same drugs delivered systematically. Feasibility studies show that the device would be safe in humans, too. These devices thus open up the potential to speed up clinical drug development and, perhaps, a way to administer personalized therapy regimens in patients.

**Summary**

The Convergence strategies in these examples include engineered nanoparticles to serve as synthetic biomarkers for cancers, enabling paper-based urine assays for early diagnosis that could potentially be used in a doctor’s office, like a pregnancy test. They also include advanced genetic sequencing tools that enable early cancer detection from a blood sample. More complex, “smart” engineered nanoparticles are the basis of emerging combination drug therapies for cancer that deliver multiple drugs at once or even two different drugs in a controlled sequence—a “one-two punch”—that optimizes their killing power against cancer and minimizes side effects. Sophisticated chemistry is behind advanced immunotherapies that activate both major components of the body’s own immune system to recognize and attack cancer. Engineering tiny, sophisticated microdevices implanted in the body enables pre-testing of drug therapies to select the optimum regime for a given individual prior to actual treatment, personalizing cancer therapies.

Most of the discoveries and new techniques described here are still in the early stages. More work needs to be done on these Convergence strategies, to refine and bring these and other new approaches into clinical practice. But the potential is clear: new, low-cost means of early detection pushed out to the doctor’s office or the clinic; safer, more efficient, more effective means of combating cancer to extend lives and lower medical costs; and new strategies to empower our immune systems to kill cancer for us.

**Other Unmet Needs**

Even if all the public health challenges described here were met, many more would remain, including:

- **Heart disease,** the number-two killer in the U.S., would benefit greatly from Convergence approaches such as wearable or implantable sensors that could monitor cholesterol levels or warn of irregular heart rhythms. If hundreds of thousands of patients wore such devices, and permitted the data they gather to be shared with their doctors, sophisticated Big Data strategies such as machine learning could identify patterns that, in specific groups of patients, would warn them of impending heart attacks or strokes. The patients could then seek life-saving treatment.

- The incidence and healthcare costs of diabetes are rising rapidly. It is increasingly clear that diabetes is a family of disorders that calls for better and more personalized therapies. Convergence approaches offer hope for preventing or even curing this chronic disease. These include biochemically engineered “smart” forms of injectable, long-lasting insulin that respond automatically to the
body’s needs; more patient-friendly ways to monitor and regulate blood sugar—via patches, pumps, pills, and other easy-to-use devices—that release drugs in response to fluctuating biochemistry; more unobtrusive ways to continuously monitor blood sugar, such as contact lenses that measure glucose levels in tears; and research to identify genetic variants that naturally protect people from Type 2 diabetes, so that therapies that mimic their effects can be developed.

- A number of inherited genetic diseases that tend to run in families need Convergence approaches. They would benefit from advanced genetic profiling to understand the specific genetic variations that cause the disease, as well as high-throughput methods to map their epigenome, the control system that activates or silences specific genes in specific cells. Improved methods of screening for such diseases early in life would allow earlier interventions, even before symptoms begin to manifest themselves. And synthetic biology approaches that turn off harmful genes or introduce missing proteins might ultimately significantly improve patient outcomes.

- Wellness: The absence of disease and the ability to live up to a person’s full potential is what everyone really wants. But we do not know how to measure wellness, or how to sort out the complex mix of diet, behaviors, environmental influences and genes that determine wellness. To give just one example, it is now clear that the human body needs both macronutrients and a wide range of vitamins, minerals, and other micronutrients—yet we have no simple, cost-effective way to assess human nutritional status. That means consumers lack the information to make informed choices about their diet. At the same time, powerful new technology—such as the miniaturized mass spectrometer on the Mars Rover—can potentially detect a wide range of minerals, metabolites, and other biomarkers in a single tiny blood sample, according scientists at the Carnegie Mellon University. Convergence processes including new measurement techniques, engagement of consumers in documenting their own behaviors via their smart devices, and the use of machine learning and other Big Data tools could transform the measurement of wellness, making possible more integrated strategies to advance both individual and broader public health.

Convergence in Other Unmet Needs

The Convergence opportunities include wearable or implantable sensors for heart disease and stroke; these in turn could enable Big Data strategies such as machine learning to optimize therapies and potentially provide early warning of strokes and heart attacks. More patient-friendly technologies for managing diabetes include “smart” insulin that automatically responds to blood sugar levels and a wide variety of new tools for managing the condition. Advanced genetic profiling, including new methods of mapping the epi-genome, could not only lead to early diagnosis, but could lay the foundation for sophisticated therapies that rewire the genes causing the disease. New measurement approaches that quickly and cheaply measure nutritional status, and engage consumers in documenting a wide range of their own behaviors and wellbeing, could enable machine learning strategies to define wellness metrics.
Endnotes

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44 Interview with Sarah Hollingsworth Lisanby, March 2016.
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Chapter 3: Crosscutting Convergence Approaches and Enabling Technologies

The preceding chapter started with major unmet health needs and gave examples of Convergence solutions. This chapter takes the opposite approach: it focuses on four broad classes of Convergence approaches—new imaging techniques, nanotechnology, regenerative engineering of tissues or whole organs in the body, and health information technology. It gives examples of both the enabling technologies that are emerging from these approaches and how they are being applied, or could be applied, to advance human health.

These technologies all stem from innovations in physics, chemistry, materials science, engineering, and mathematical and computational science—and, often, combinations of these disciplines. The examples discussed here are hardly exhaustive—many more areas are relevant to improving human health. The areas chosen do suggest the power of Convergence strategies in research, both to advance basic knowledge and to improve human health, often dramatically. The broader question at issue is whether a conscious, coordinated effort at Convergence across these disciplines could develop even more powerful solutions, hasten their availability, and integrate the resulting knowledge to enhance human health and wellbeing.

Imaging in the Body

Introduction

Seeing inside the body has enabled both fundamental research and medical practice ever since the discovery of x-rays more than a hundred years ago. Today clinicians routinely use x-rays, microscope examination of tissue samples, x-ray computed tomography (CT) scans, magnetic resonance imaging (MRI) and ultrasound imaging, and a variety of optical imaging technologies including endoscopy, intra-operative imaging, and optical coherence tomography to help them diagnose disease and guide treatment. Research scientists seeking to understand the workings of cells, specific tissues and organs also use advanced optical, fluorescence, and electron microscopy, mass spectrometry, bioluminescence, and a rapidly expanding range of novel and powerful imaging tools.

All of these imaging techniques are based on physical principles; they require precision engineering and often novel materials to create useful tools, and depend on chemical and biological insights—and increasingly on mathematical algorithms and Big Data analytics—as well as medical expertise to interpret the results.

Advances are needed because greater spatial resolution—the ability to see individual cells or even cellular components—is often essential to an accurate diagnosis or greater understanding of biological processes. But many high-resolution techniques, such as optical microscopy, cannot see deep inside the body. At the same time, imaging techniques such as CT scans and MRI that can see deep within the body or a given tissue are extremely useful, but often lack high spatial and soft tissue resolution. Other key characteristics of an imaging method include sensitivity, throughput (the ability to image many objects very quickly), ease of multiplexing (combining data from multiple sources or events), and, of course, cost. Convergence approaches could optimize existing techniques across these criteria and accelerate the development of new methods that achieve these characteristics more fully, with the potential to open up entirely new areas of knowledge. Recent Convergence-driven innovations illustrate the potential both to discover new biological insights and to enhance the interpretation and value of existing clinical datasets and tissue samples related to wellness and disease.

Recent Advances

Molecular Imaging. A major imaging challenge is the simultaneous detection in cells and tissues of many biochemical markers and genes that contribute to biological function and disease. The current gold standard for imaging such molecular markers makes use of fluorescent
molecules attached to antibodies, which bind to specific targets on cells and tissues; fluorescence microscopy can then detect the marked cells or tissues. This antibody “staining” technique is used widely throughout biomedical research to detect specific molecules and to quantify molecular interactions in cells and tissues, but can detect only a handful of markers at the same time because of spectral and spatial overlap of the fluorescing molecules. Complex diseases such as cancer typically involve more than just a few molecules and their interactions—so better solutions are needed. Promising emerging solutions include:

• **Multiplexed ion beam imaging (MIBI)**. This technique, developed by a collaboration of pathologists, engineers, and biologists from Stanford University and the University of California-Davis, utilizes antibodies tagged with metals rather than fluorescing molecules. When the tagged antibodies bind to proteins and genes of interest, their presence and location within a tissue can be detected with ion mass spectrometry, which is sensitive to the metals. More than 100 isotopically-pure metals can be used as tags, enabling the researchers to detect and locate simultaneously as many as 100 clinically important molecules in a cell or tissue sample. The MIBI imaging technique can also reveal the spatial features of protein expression in individual cells. The researchers are now utilizing MIBI to study the complex interactions between cancer cells and their microenvironment—which includes immune cells and non-malignant stromal cells that form the structural framework of the tumor—to understand how the microenvironment influences tumor cells to grow and metastasize throughout the body.

• **Multiplexed error-robust fluorescence in situ hybridization (MERFISH) and Fluorescence in situ sequencing (FISSEQ)**. These two techniques have made it possible to detect the presence and location of numerous RNA species in a cell and then to measure quantitatively which genes are active; this can provide information about which proteins are being synthesized in a particular cell. MERFISH, developed by biologists and physicists at Harvard, uses combinatorial labeling of RNA with error-robust encoding schemes and then sequential imaging to detect the copy number and location of thousands of RNA species in individual cells in situ. Tens of thousands of cells can be measured in a single day of MERFISH experiments. FISSEQ, developed by biologists and engineers at Harvard and the University of California-San Diego, identifies the RNA directly within intact cells and tissues using next-generation sequencing, in effect creating a map of gene expression at the cellular and subcellular level. These techniques can process many cells very quickly—they are high throughput techniques—and have already identified hundreds of specific RNA genes active in human skin cells. Connecting such imaging technologies to pathology data could allow understanding of how different cells react to different therapies for highly heterogeneous diseases like cancer. These techniques offer the potential of mapping all RNAs in the body at single-cell resolution—in effect, creating an atlas of cells sorted by which genes are active in them—and thus provide a new level of understanding of the functional output of our genetic system and the molecular basis of diseases.

**Whole Organ Imaging.** A fundamental challenge in the field of biomedical imaging is the ability to extract structural and molecular information from intact organs. The traditional method of obtaining information from intact biological systems requires slicing organs into thin sections of tissue that can be observed using conventional light and fluorescence microscopy techniques, but that loses a lot of data about the three-dimensional structure of the organ. This challenge is particularly important for the brain, perhaps the most important but least understood organ, given its three-dimensional complexity and the intricate connections between neurons. Imaging of intact organs at
the molecular scale would be a great advance for biomedical research. An unorthodox Convergence approach is already yielding promising results.

• **CLARITY.** Combining neuroscience and chemical engineering, scientists at Stanford University have developed a technique that renders intact brains optically transparent. The method, called CLARITY, infuses a brain with a hydrogel that binds to proteins, nucleic acids, and other molecules. The gel is then catalyzed to form a polymer that secures the biomolecules in place. Then, using detergents, the technique dissolves and extracts the opaque elements of the brain, primarily lipids. The treatment leaves the organ intact but optically transparent, enabling study of the brain’s three-dimensional fine wiring and molecular structures using visible light microscopy and chemical markers. Researchers have already used this method to probe cells and tissues from intact mouse brains—from the outer layer into deeper structures such as the thalamus. CLARITY opens up the possibility of imaging and extracting complex 3D information from healthy and diseased human brains from tissue banks across the world. Its application to any biological system would enable the study of all organs in their intact form.

**Whole Body Imaging.** The convergence of disciplines in chemistry, material science, biomedical imaging, computational sciences, applied physics, and engineering (electrical and chemical) is providing new methods of whole body imaging in people. Already, two novel techniques have emerged:

• **Raman spectrometry.** This spectroscopic method has long been used by chemists and materials scientists as an analytic tool for chemical analysis. It relies on the fact that, when a light is shined on a sample, a small amount of it scatters “inelastically”—meaning that the wavelength of the light reflected back is different from the incoming wavelength. The inelastically-reflected wavelength is characteristic of the molecules in the sample. This phenomenon has only recently been applied to imaging. To do so required collaboration of physicists (who understand the Raman process), material scientists (who understand how to amplify the signal it sends), chemists (expert at imaging agents that go into the body and latch onto a molecular target), and engineers (to build the equipment). Raman imaging allows researchers to interrogate multiple events at the same time, with high sensitivity and great spatial resolution, down to a single cell. The technique is used for imaging of molecular interactions in cell populations and of preclinical animal models. It has also begun to be used clinically to image the gastrointestinal (GI) tract and guide surgical procedures, as well as to diagnose cancer, particularly breast tumors.

• **Photoacoustic imaging (PAI).** This technique relies on an effect first described by Alexander Graham Bell, who invented the telephone. Bell found that when a focused beam of light is rapidly interrupted and allowed to fall on a block of selenium metal, an audible signal could be picked up through a hearing tube. In PAI, a laser is used to pulse light into the body, interacting with molecules, causing them to heat up. This leads to pressure waves that produce sound, which in turn can be converted into an image. The combined use of light and sound in this type of imaging has an important advantage over many other imaging techniques, because it provides high spatial resolution as well as depth penetration, and because the imaging process does not require the use of an imaging agent such as a fluorescent stain. PAI is now used to image living tissue in small animal models as well as in people. It is being tested to determine its effectiveness in detecting cancers of the breast, prostate, bladder, skin, ovary and
thyroid—and of tumor cells that circulate in the blood. PAI can also be used to image and characterize changes in the eye that occur during diabetic retinopathy, age-related macular degeneration or glaucoma, as well as to image the thyroid and the GI tract.

These examples illustrate the potential power of Convergence approaches to imaging for fundamental research—to better understand biological systems on a molecular level (including identifying specific genes and proteins), as entire organs, and as whole body processes. The examples also suggest the power of such Convergence research strategies to develop transformative solutions in cancer, diabetes, immune system function, brain disorders, and a wide variety of additional areas that can improve human health and wellness.

Nanotechnology for Drug & Therapy Delivery in the Body

Introduction

Nanotechnology is about very small things—particles small enough that thousands could fit on the period at the end of this sentence—and hence small enough to be carried around the body in the bloodstream. This technology is being used to fashion complex, carefully-engineered nano-carriers that target specific cells, tissues or organs to deliver drugs and other therapeutic packages. Such engineered nanoparticles can also detect disease or even directly kill cancer cells with minimal side effects. Gene silencing. One of the most powerful uses of nanoparticles is to deliver snippets of genetic material—small RNA molecules—that can interfere with and turn off specific genes in target cells. Recent research shows that such interfering RNA can be packaged in polymer nanoparticles comprised of three or more concentric spheres made of short chains of a chemically modified polymer. These complex nanoparticles can deliver their RNA therapy to silence diseased cells of the type that form blood vessels and the linings of most organs. This is important because such cells contribute to more diseases than any other tissue in the body, including atherosclerosis and diabetic retinopathy, which can cause blindness. The specificity of delivery is also important—most strange particles in the bloodstream is gathering momentum, with more than a dozen clinical trials in process and strong evidence of success in delivering sophisticated therapies to the liver, brain, specific types of diseased tissues, and cancer cells.

One key motivation for some of this work was the discovery, in 1998, that short pieces of RNA inserted into a cell could interfere with—and turn off—specific genes, thus blocking the manufacture of the protein for which that gene codes. But getting such interfering RNA to specific cells proved extraordinarily difficult. Actually, drug delivery of any kind via the blood stream is not easy. Many potential therapeutic agents are not soluble in blood. Moreover, the immune system and the liver tend to capture foreign particles, preventing them from reaching their targets. And drugs or other therapies intended for the brain must pass through the blood-brain barrier, which keeps out most larger molecules, such as proteins or peptides. To solve such challenges requires a Convergence approach. In effect, the challenge is to design a suitable nanoparticle carrier, load the therapeutic package into it, direct it to the right tissue or organ—and often to the right target in a specific type of cell—and then to control the release of the active agent.

Recent Advances

Gene Silencing. One of the most powerful uses of nanoparticles is to deliver snippets of genetic material—small RNA molecules—that can interfere with and turn off specific genes in target cells. Recent research shows that such interfering RNA can be packaged in polymer nanoparticles comprised of three or more concentric spheres made of short chains of a chemically modified polymer. These complex nanoparticles can deliver their RNA therapy to silence diseased cells of the type that form blood vessels and the linings of most organs. This is important because such cells contribute to more diseases than any other tissue in the body, including atherosclerosis and diabetic retinopathy, which can cause blindness. The specificity of delivery is also important—most strange particles in the bloodstream
are swept up by the immune system or the liver, but these nanoparticles did not turn off genes in liver or immune cells. With the best-performing particles, researchers at MIT reduced gene expression by more than 90 percent with an extremely small dose. They also showed that they could block up to five genes at once by delivering different RNA sequences.

Packaging “interfering RNA” molecules in a different way—changing the chemistry of the nanoparticle—may enable delivery to different parts of the body. Researchers are still busily creating thousands of different chemistries and seeing where the nanoparticles end up. Nanoparticles made of lipopeptides, for example, have enabled precise targeting and silencing of liver cells without significantly affecting immune cells or causing other side effects. Still other efforts are underway to package RNA in a way that could pass the blood-brain barrier and thus target genetic disorders in the brain. Commercial efforts are already underway to develop nanoparticle therapies for hepatitis B, hemophilia, and high cholesterol. And a strong possibility, researchers say, is the use of RNA-containing nanoparticles to treat cancer by turning off the run-away genes without chemotherapy or radiation.

Immunological Shielding. A major problem in utilizing nanoparticles to deliver therapeutics to target tissues within the body is that they are often attacked by the body’s own immune system. For example, nanoparticles delivered in the bloodstream are often cleared into the liver, where immune cells swallow the majority of the therapeutic that is delivered. In fact, the majority of immune cells within the body recognize nanoparticles as foreign invaders, much like bacteria, and act to remove them from the body. One way around this problem, devised by a team of bioengineers and oncologists, is to camouflage nanoparticles from the body’s immune system by coating them with membranes of cell fragments known as platelets, which naturally flow in the bloodstream and are responsible for blood clotting in response to injury. The coated nanoparticles are able to evade detection by the immune system. The platelet membrane coating has another beneficial feature: it preferentially binds to damaged blood vessels and certain pathogens such as MRSA “super bug” bacteria, allowing the nanoparticles to deliver and release their drug payloads specifically to these sites in the body. Enclosed within the platelet membranes are nanoparticle cores made of a biodegradable polymer that can be safely metabolized by the body. The nanoparticles can be packed with antibiotics or other small drug molecules that diffuse out of the polymer core and through the platelet membrane onto their targets. The technique delivers a much higher dose of medication to diseased tissues without saturating the entire body with drugs.

Nanoparticles and the Brain. Nanoparticles are a very promising approach to outwitting the blood-brain barrier and thus delivering therapies to the brain. In effect, these particles with a neutral outer surface of polymers shield the active agent—such as a protein or a piece of an RNA molecule—while it is delivered into the brain. These can be designed in several different ways, depending on the specific target. These include:

- nanoparticles that slowly dissolve, releasing their therapeutic package at a controlled rate;
- nanoparticles that are stable until they interact with a specific target inside a cell, which releases their package;
- nanoparticles that remain stable, but allow their package (such as an enzyme) to be active and deliver its therapeutic effect from inside the nanoparticle;
- nanoparticles that are loaded into immune cells that carry them to the site of disease in the brain where they release their therapeutic package.

The goal is to be able to control all aspects of the therapy that nanoparticles deliver—timing, dosage, and physical action. That, in turn, requires mastery of the physics of
these tiny objects and the engineering of their manufacture and loading with their therapeutic packages. It can require polymer chemistry to create the nanoparticles in ways that make them compatible with or attracted to specific tissues in the body. And it may require the generation and use of low-frequency alternating magnetic fields to trigger release of a therapeutic package—thus enabling the brain, for example, to manufacture a critical protein. This is a rapidly-moving area of research, with very promising potential.

**Nanoparticles and Cancer.** Treating cancer is one area where “interfering RNA’s” particular advantages are expected to shine. Conventional chemotherapy affects more than just the target cancer cells—it also hurts healthy tissue, which is why it makes people feel miserable. But RNA packages can be extremely precise, potentially shutting down only the genes making proteins found in cancer cells. And recent laboratory research into advanced nanoparticle delivery systems makes it possible to target up to 10 proteins (and the genes that make them) at once, which could make cancer treatments far more effective. Lab work like this is still far from a proven therapy, but if it maintains its momentum, the drugs currently in clinical trials could represent just a small portion of the eventual benefits. (See also the Cancer section in the preceding chapter.)

**Mechanical Activation.** One of the unsolved challenges is precise control of the release of a therapeutic package from its nanoparticle carrier when it reaches its target. An intriguing area of research is the use of low-frequency alternating magnetic fields generated outside the body, which penetrate the body without causing harm, to trigger such release. In effect, the alternating magnetic fields would activate or vibrate small nanoparticles that act as tiny magnets and could be used to control drug delivery, either by themselves or in combination with local heating caused by magnetically generated electrical currents. These approaches may create new therapeutic opportunities.

A more direct potential application of magnetic-mechanical activation involves cancer. The idea is to use the unusual magnetic properties of tiny iron-nickel magnetic disks. These disks, coated with a thin layer of gold, are not magnetic until placed in a magnetic field. When an alternating low-frequency field is applied, however, the disks rotate rapidly and damage the surrounding tissue, effectively killing the cell. Thus they could potentially provide a targeted therapy for cancer cells that does not involve toxic chemicals.

*These examples illustrate the potential power of Convergence approaches involving nanotechnology to transform drug delivery and enable advanced therapies for a wide range of human disease. Such research would also advance basic understanding of many areas of biology.*

**Regenerative Engineering and Medicine**

**Introduction**

If salamanders lose their tails or a leg, they can regrow them at any point during their lifetime. What if people, too, aided by advanced regenerative engineering strategies, could also regrow damaged or amputated body parts? Think of all the wounded warriors, the failing knees of an aging population, the long waiting lists for transplanted kidneys. There have been significant advances in prosthetics—electromechanical replacement limbs—but they still do not restore the sense of touch and normal feedback in movement. Organ transplant techniques have also improved, but infection and rejection of the alien tissue are still significant problems, quite aside from the huge shortage of donor organs. But people do continuously regrow both skin and blood cells throughout their lives—so why not more complex tissues or whole limbs?

In fact, advances in regenerative engineering offer the hope of bringing these techniques into routine clinical use. Already, artificial skin developed for burn patients is widely used. New techniques to foster bone growth are on the market. And more significant opportunities are emerging, some already in clinical trials.
These new approaches define Convergence: they require sophisticated new materials compatible with the human body to provide a lattice for new tissue to grow on; the use of adult stem cells derived from the patient to generate new tissue that won’t be rejected; advanced developmental biology to stimulate cell and tissue growth; carefully engineered bio-reactors to provide nutrients and controlled growing conditions; clinical translation; and even genetic approaches to turn specific genes on or off. Recent innovations illustrate the potential for such convergent approaches.

Recent Advances

Bioprinting. One area of importance for regenerative engineering is the use of adult stem cells, which are found in fat, blood, and other parts of the body, or even in ordinary skin cells that have been re-programmed to act as stem cells. Such cells—unlike those from developing embryos—are easily obtainable from a patient and can be stimulated to grow into new tissues. They can be loaded into a 3D printer cartridge, allowing new tissues to be printed in the sizes and shapes desired, or simply “painted” onto an existing protein structure, placing millions of cells in a very short time. This makes it possible, in principle, to regrow damaged parts of the body with tissue that the body recognizes as its own—in effect, to harness the body’s own internal healing mechanism, and to accelerate it.

Ligaments and Tendons. Some 200,000 people tear an anterior cruciate ligament (ACL) every year in the U.S. alone. Surgeons can repair these by transplanting a tendon from elsewhere in the patient’s body or from a cadaver, but it doesn’t always work. Recent work at the University of Connecticut shows that it is possible to prompt the body into re-growing the ligament. The approach utilizes the torn stump of the ACL, which contains stem cells, other tissues, and nutrients needed for regrowth. A specially engineered matrix is implanted that provides immediate support for the knee, but also a structure for cells to attach to and grow on. Then a specialized bioreactor is placed around the knee for 12-18 months to protect the growing tissue and provide additional nutrients. After successful experiments with rabbits and sheep, the new engineered ligament is now in human clinical trials. A similar approach is underway to regrow injured Achilles tendons. A biodegradable polymer is used to supply stem cells (obtained from fatty tissue) and growth-stimulating peptides to the injured site, enabling the stem cells to develop into tendon tissue and regrow the tendon.

Growing Whole Organs for Transplant. Another area of active research is growing whole organs. The need is clear—at any given time in the U.S. more than 100,000 people are waiting for transplants of various kinds. The ideal is to take cells from the patient and regrow an organ that could then be put back into the patient. That may well be possible for relatively simple organs—already, in a few cases, replacement bladders and veins have been made to work...
successfully in animal models and in a few humans. But for more complex organs—livers, kidneys, hearts—several researchers at Massachusetts General Hospital and the Texas Heart Institute are following a different approach. They start with donated cadaver organs, then wash away all of the donor’s cells, leaving only the structural protein framework of the organ, typically composed mostly of collagen. Then they add cells from the intended recipient with nutrients and growth factors, and let the new organ tissue regrow on the collagen structure. That is much simpler, in principle, than trying to create all of the tiny microtubules in the kidney, or the precise structure of arteries and valves in the heart. And the resulting organ would be immunologically identical to the recipient, so there are no rejection risks—it would be like getting a new heart that is really your own.

Success is not assured, but the potential is a much larger supply of transplantable organs than could ever be obtained from living donors. Indeed, the donor organ does not even have to be from a human; pig organs seem to work fine and are often stronger and healthier than those from human cadavers. But scientists are still sorting out which kinds of cells work best. The sheer numbers are daunting—the heart has billions of cells. And getting the new cells to take root on the protein structure and grow, and then to become functioning parts of a beating heart, is trickier. So researchers put the heart in a bioreactor engineered to mimic the sensation of beating with a pump, and often use electrical signals to help synchronize the actions of the individual cells. In animal experiments, some hearts eventually beat on their own, if not yet fully efficiently. The final challenge will be to implant such a heart and connect it to all the vascular plumbing of a living animal or human. At the very least, scientists doing this work expect to learn a lot about the cell types within organs and how they work together, which may suggest still other therapeutic approaches.

Restoring Organ Function. Whether or not complex organs can be regrown, there is another approach that could significantly improve human health. It stems from the recognition that the human body has remarkably redundant capacity. Organs such as the kidney or the liver can function even with only a fraction, perhaps 10-20 percent, of their normal capacity. In fact, symptoms of organ failure in a patient usually don’t occur until that point. So the idea being pursued by researchers at Wake Forest University is to insert a wedge of healthy tissue, equal to 10 or 20 percent of the organ, in such patients to keep them alive with a high quality of life.

For a patient with kidney failure, for example, the process might go something like this: extract some healthy kidney cells from the patient and grow them; remove cells from a healthy pig kidney, leaving only the protein structure; then repopulate the pig organ with the patient’s cells. Insert a segment of the new kidney tissue into the patient’s failing organ, where it is recognized and accepted as “self” and can quickly begin to function. In principle, such partial transplants are much easier, and perhaps more likely to work, than re-growing whole organs. This approach is not yet in human clinical trials, but animal trials already show promise.

These examples illustrate the potential power of Convergence approaches that combine developmental biology, bio-engineering, and clinical innovation to dramatically improve the quality of life for those with damaged or dysfunctional body parts. The same research efforts will also advance basic understanding of the developmental process that generates the organ in the first place. For example, to make synthetic organs will require stem cells with the right structure and signaling characteristics, so that these cells generate the complex tissues needed to function as bone or tendon. The nature of signaling between muscle, vascular, and neuronal tissue, currently poorly understood, can be studied in these synthetic organ bioreactors. In another area of science, these types of organ...
Convergence science will not only advance innovations in healthcare but will also advance fundamental knowledge of biological systems.

**Big Data & Health Information Technology**

**Introduction**

The idea of precision medicine—that we could know exactly what is wrong with a person and so precisely determine how to treat their condition—is very attractive. But the reality is that such precision is today really only available, even in part, for cancer, because most cancers have a strong genetic component and years of research on the human genome have begun to provide insights. Human health, however, depends not just on genetic factors, but even more critically on environmental and behavioral factors—what we are exposed to, what we eat, our lifestyle choices. And consistent data that allows comparison of these factors—what medical data scientists would call stratifying the phenotype—simply doesn’t exist for large numbers of people, not in electronic medical records, not anywhere.

Partly this is due to the many different and incompatible electronic medical record systems, but it is more than that. Diabetes, for example, is not a single disease but rather a collection of many different conditions that result in high blood sugar. People with diabetes, not surprisingly, often react very differently to the bewildering array of different medicines and treatment regimens now available, as well as to different diets and different environmental conditions.

The challenge is actually even more difficult, because the real goal is to understand what it means to be well, to function at the peak of our physical and mental capabilities, as well as to prevent or deal with illness. And while we know a lot about how to diagnose illness, we don’t know how to diagnose or measure wellness, which means that most preventive advice exists only as generalities: eat more vegetables, get more exercise, get enough sleep.

So the challenge—and the opportunity—is to use Convergence research strategies to improve this lack of meaningful, comparable, scientifically-useful data and to develop advanced means to analyze such data.

**New Opportunities**

**Consumer-focused Health IT.** Addressing modern health challenges requires an improved understanding of wellness before onset of disease, as well as key signals of disease. To achieve that requires active consumer input of data on their health and lifestyle (such as blood sugar measurements and diet), but also passive data collection (with consumer consent). Passive data might include continuous measurements of environmental influences such as changes in the microbiomes or exposures to air- or food-borne toxins; physiological measurements like blood pressure and heart rhythms; and behavioral assessment tools like FitBit apps that can measure physical activity. In the near future, self-powered implanted sensors could monitor far more variables and report data wirelessly to smart phones, which also can track consumer locations and activities (again, with consumer permission). A number of these applications developed by MIT, Stanford, and other universities are now being implemented in smartphones, explicitly for research purposes. Consumers in large numbers are volunteering their data, potentially making smartphones the most impactful medical device in the history of the world.\(^{110}\) The integration of health apps with electronic health records, like the SMART app platform will be critical for data-driven insights into health.\(^{111}\)

The Convergence of smart mobile devices, advanced diagnostics, and deep learning algorithms to mine the data can play an important role in the development of passive methods for gathering physiological and other health information from patients. Additional passive data
High Throughput Molecular Profiling. Consider the potential for personalized immunotherapy—treatments designed to boost the body’s natural immune system to fight infection and disease—in the form of personalized cancer vaccines, for example. Many cancers are genetically unstable; as a result, each patient may have a unique disease state that changes over time. But by measuring the protein-encoding genes in that patient and protein fragments containing cancerous mutations that are often present on the surface of cancer cells, it would be possible to create a personalized cancer vaccine containing multiple antigens that would enable his or her T-cells to recognize and attack those cells. Identifying the most promising antigen candidates—as well as finding ways to measure the resulting therapies’ effectiveness—will require quantitative and very rapid single-cell analysis. Developing and deploying this technology will in turn require a combination of basic biological knowledge, next-generation sequencing, in situ gene expression profiling by imaging, computation, analytical chemistry, and machine learning.

What is promising about this approach is that—in contrast to clinical trials that require thousands of patients—it can be based on trials that contain only a single or very few patients (especially those who respond very well to specific therapies), but include a large amount of data from each patient. For example, sequencing a large number of a patient’s T-cells and identifying the antigens which each recognizes would provide a much better understanding of how the immune system is fighting infection and disease. Combined with a broader program to identify cellular patterns within a tissue—where in space the cells exist, and how that varies between healthy and diseased tissue—it could lead to the development of generalizable therapy platforms that are broadly deployable, even if the specific therapies differ for every patient.
Documenting Environmental Exposures. High throughput techniques combined with advanced mass spectrometry would also be crucial in creating a rapid way to assess individual human exposure to environmental health factors, including those acquired by individual behaviors. In principle, a blood sample contains a record of that exposure—to prior infections, to environmental antigens and toxins, to microbiome chemicals and nutritional metabolites from the diet. If our genetic heritage defines our “nature,” these biological markers are the “nurture” part of human health. They account for a majority of human disorders as well as play a major role in overall wellness.

We now utilize and measure more than a billion features of the human genome; sequencing an individual genome costs less than $1,000. Mapping and quantifying environmental exposure would require identifying an estimated one million biological markers—an effort equivalent to establishing the human genome sequence database, but easier now because of advanced technology. Linking these biomarkers to their environmental causes would provide an “exposome” reference to which individual biomarker patterns could be compared. Machine learning techniques would then permit the discovery of predictive patterns that could begin to establish a more empirical basis for personalized preventive and treatment measures. The result would be a more complete knowledge of the chemistry of nurture, of life as it is really lived amidst a complex and changing array of foods, industrial chemicals, environmental toxins, and infectious agents.

What is especially exciting about these opportunities is the potential to gather, inter-compare and relate genetic, environmental, and behavioral data gathered from millions of people.
Endnotes


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Introduction
The Convergence Revolution is making tremendous strides. Cancer diagnostics—from quick urine tests that identify early-stage tumor growth to miniaturized components of hand-held devices that allow magnification and imaging of cancer cells in real time—will help millions of people across the world live longer while concurrently increasing their quality of life and enhancing their capacity for productivity. Advances in cellular engineering are leading to a day when brains damaged by stroke or traumatic injury may be repaired and lost limbs regrown. Through nanotechnology research, the tiniest of devices will deliver drugs to highly specific targets.

These advances and many others are being made possible by the collaboration of experts across multiple fields. These experts are combining the power of imaging, computational and computer science, cellular and molecular engineering, modeling, and other technologies to produce inexpensive, rapid diagnostics; generalizable and personalized vaccines; the redesign of existing natural biologic systems; new, biologically-based manufacturing methods and drugs; and individualized treatments.

But the transition from laboratory to market is expensive and slow, and many promising discoveries fail to make their way to adoption. U.S. biomedical industries face regulatory and workforce obstacles and increasing competition from abroad. Most American universities are not designed for Convergence education or research, and siloed government agencies distribute biomedical research funds that remain below 2003 levels when accounting for inflation. In this chapter, we describe some of the challenges that must be met by industry, academia and government if the Convergence Revolution is to achieve its full potential.

Industry Challenges
The Convergence Revolution is transforming science and medicine and contributing to an industrial ecosystem that is streamlining research and development, lowering costs, and improving patient care. In that ecosystem, some companies supply Convergence products and technologies for research. Others use Convergence technologies to discover and develop drugs, diagnose illness, or monitor health and wellness. Still others provide data analytics technology and capabilities that fuel biomedical innovation or enhance care in a variety of settings. All are affected by a changing paradigm in which "powerful trends of new technology, demand for value, a growing health economy and government influences are transforming the U.S. health care market." 120

In light of aging populations, increasing prevalence of chronic disease, and population growth in the developing world, analysts predict considerable growth for many life science companies, especially those in Convergence fields such as companion diagnostics; precision medicine; those combining therapies, drugs, diagnostics, disease management and clinical support; and those supplying digital health technologies and analytics. Growth is also expected in biotechnology fields fueled by advances in tissue regeneration, nanotechnology,121 and DNA sequencing; for biological products such as vaccines, gene and cellular therapies, human cells and tissues used in transplants; for in vitro and neurodiagnostics; and neuro- and cardiovascular imaging.122, 123

Global markets for mobile health applications, sensor technology, informatics, data analytics, and artificial intelligence are also experiencing rapid growth. The global market for wearable devices—especially remote monitoring—is expected to expand at a compound annual growth rate of 16.4 percent from 2013 to 2019. The overall market for wearables, worth $2 billion in 2012, is projected to reach a valuation of almost $6 billion by 2019.124

Today, the U.S. is a global leader in many of the above arenas and health technology is a major and growing part of the U.S. economy. Despite increasing competition from abroad, the U.S. can solidify—and advance—its leadership
status. But this is not an issue of economic nationalism—world health needs a continued strong American role.

In the 1950s, U.S. research led to major advances in treating heart disease—imaging technology, stents, medications such as statins, and tools for interventional cardiology—which contributed to a 75 percent reduction in coronary heart disease deaths between 1963 and 2010. Today, U.S. companies are poised to accelerate their leadership roles, especially in neuroscience, data, nanotechnology, and drug development and delivery systems.

But in order to accelerate momentum, U.S. biomedical industries need to meet a variety of challenges. Those challenges, which vary by industry segment, include, among others:

- The time it takes to bring bio-inventions out of laboratories, up to scale, and into markets.
- Increasing costs and shrinking federal and corporate investments for research and development, especially in early stages crucial to innovation, as well as the costs and complexity of clinical development.
- A “blockbuster drug” economic model that does not fit many Convergence technologies and approaches.
- Outdated information technology infrastructure; incompatible data sets that cannot link to each other; limited Big Data analytics and predictive analytics capabilities; the complexity of R&D informatics; privacy and security concerns; and, simply, the management and interpretation of massive amounts of data.
- Regulation, compliance, and pricing across multiple geographic regions; foreign competition; economic instability; and a lack of profitable business models for advancing health care in poor nations.
- Educational pipelines not calibrated for next-generation industrial needs, company cultures and structures that do not match up with or foster Convergence innovation.

For American industry to surmount these challenges and maintain its leadership position in international discovery and biomedicine, this nation must first address two major underlying problems:

1. A shortage of workers with capabilities in Convergence scientific, medical, and bioengineering fields, and
2. Inadequate funding for early-stage research.

Below, we discuss educational and governmental changes needed to resolve those two problems.

**Educational Challenges**

With increasing Convergence in industry and research, there is a growing need overall for capable employees in burgeoning biomedical-related fields. Between 2014 and 2024, the U.S. Bureau of Labor Statistics projects 23 percent growth in bioengineering jobs; 15.4 percent to 20.9 percent job growth in computer and information science and systems fields; 15.9 percent growth in jobs for most physicians and surgeons, and a remarkable 33.8 percent increase in jobs for statisticians.

In fact, while workforce needs may vary by scientific field, the President’s Council of Advisors on Science and Technology projects a need for one million additional STEM professionals by 2022. And, according to a 2013 report by the McKinsey Global Institute, the U.S. could face a shortage of 190,000 data scientists by 2018. Even now, pharmaceutical, biotechnology, and other scientific companies are struggling to find employees with the requisite computational and data skills integrated with their life science skills to work collaboratively on Convergence projects. On the other hand, endless growth in biomedical science fields themselves cannot be assumed. The pressure of declining funding discussed below has led to a highly competitive system that is tending to discourage outstanding researchers by limiting access to support for their research. There is a danger of science talent decline which requires addressing, despite societal demand for biomedical-related sectors overall.
To support growth in biomedical Convergence fields, it is crucial that U.S. colleges, engineering, and medical schools graduate students with skills in information science and knowledge in multiple scientific or technical disciplines. But, despite federal and academic efforts, many American students are not being adequately prepared for careers in Convergence industries. Increasing the number of graduates in relevant fields is not enough; we must focus on changing education so we prepare students to learn and work in a world of Convergence.

Grades K-12

The workforce skill problems in the U.S. begin early. The Federal government’s ambitious five-year initiative promoting STEM in grade, middle and high schools is now halfway toward achieving its goal of preparing 100,000 new math and science teachers by 2021. However, 50 percent of U.S. high schools still do not offer calculus; 27 percent do not offer physics; and 10-25 percent of high schools fail to provide at least one core science subject, such as algebra I and II, geometry, biology, or chemistry. By some estimates, just one quarter of all K-12 schools in the U.S. offer computer science with programming and coding. Basic skills in all these fields are relevant to Convergence, which must draw on the whole, not just one element.

But numbers are not the only issue. Preparing students for Convergence must start early through new curricula and course design. The National Academies’ Framework for K-12 Science Education calls for exposing all students to engineering design, for example, and for crosscutting STEM learning across fields. This Framework is the basis for the Next Generation Science Education Standards now being considered in many states. NSF and the White House have also launched a new initiative—CS4All (computer science for all)—to make programming and computing skills pervasive in K-12. Promising examples are emerging, like the Dos Pueblos High School Engineering Academy in Santa Barbara, CA.

Colleges and Universities

Certificate and associate degree levels

Many of the most needed workforce technology skills are at the middle level. A Brookings Institute study indicates that 26 million U.S. jobs require a high level of knowledge in a STEM field, and half of STEM jobs are available (in labs, industries, and medical facilities) to workers without a college degree, where they receive substantially better pay than for jobs with similar education requirements. Implementation of Convergence research and results will require innovative, creative mid-level skills workers and new cross-field course offerings to fill these needs.

Undergraduate level

In colleges, over 40 percent of entering students who say they plan to major in STEM fields pursue other fields or drop out of college entirely, placing the U.S. at a competitive disadvantage. In contrast, in China, nearly half of all first university degrees (49 percent) awarded in 2012 were in science and engineering, compared with 33 percent in this country. While there is a high rate of switching of majors in U.S. colleges in non-STEM fields as well, the STEM switching and dropout rates are particularly severe among students from underrepresented minorities or low-income families, resulting in a serious talent loss.

Globally, the number of first university degrees in science and engineering reached about 6.4 million, according to the most recent estimates. Almost half of these degrees were conferred in China (23 percent) and India (23 percent); another 21 percent were conferred in the European Union; and just 9 percent in the United States. And, while the U.S. now graduates 25,000 more engineers than it did in 2009, it is shocking that the European Union, another developed economy, graduates twice the number of engineers per capita as does the U.S. The Federal STEM Education 5-Year Strategic Plan marked a significant policy effort to turn around STEM graduate rates.
Apart from the numbers, a critical point is that, despite the growing importance of Convergence in research, medicine, health care, and industry, most university structures remain siloed along traditional departmental lines, making it difficult for students to develop skills needed to succeed in Convergence fields. While certain schools have developed new structures and teaching methods, many undergraduate institutions still lack the capacity to offer deep foundations in math, physical, and information science along with understanding of the strengths and limitations of different disciplines, especially in the biomedical sciences.149

To encourage interdisciplinary collaboration among students, faculty, and researchers, universities need to create “cultures of Convergence” and promote new ways of solving problems. One day, individuals may have deep expertise in fields that cut across today’s traditional departmental boundaries. But for now, universities need resources and structures that allow solutions such as team teaching or research, in which, for example, a biologist and an engineer might join forces to teach a course in genetic engineering or in which a biology student and an engineering student would be paired to solve a research question.

Graduate and Post-Doctoral level
In 2014, the U.S. awarded some 40,500 doctoral degrees in science, technology, engineering, and mathematical fields.150 A small proportion of those PhDs were conferred by programs that allow graduate and post-doctoral students and researchers from different fields to work together on complex problems. But most came from institutions of higher learning not yet equipped for Convergence research or training, with notable exceptions highlighted in Chapter 1. In part, that is because Convergence educational models are complex. They require considerable funding, teaching, and research teams that cut across traditional disciplinary boundaries, shared physical space, and curricula that balance specialization with breadth of knowledge. What is more, in this transitional period, it is not clear how students educated in Convergence approaches will be welcome in industries, academic, and research organizations still organized along traditional lines, and in which deep specialization is required for hiring and promotion.151

Recommendations for modernizing U.S., graduate education in the Federal STEM Education 5-Year Strategic Plan embrace a Convergence-type approach of better preparing graduate students for a range of career paths, not only in academia, noting that “well-prepared graduate students” must have disciplinary depth but be fluent with a range of related fields.152 For Convergence to work as a research model in the health field, graduate education is a particularly critical stage since research leaders will emerge from graduate programs. Susan Singer of NSF has proposed a series of steps for Convergence education that are relevant here, including: developing a “Convergence creole”—a new vocabulary—to capture and convey core ideas across fields; using online courses with assessment and feedback features to scale education in Convergence basics; a focus on interpersonal skills to improve collaboration across fields; and developing proven metrics for measuring success in acquiring Convergence concepts.153 Similarly, the National Academies have made proposals for advancing new education modules to advance Convergence research.154 NSF’s Research Traineeship Program (NRT—formerly IGERT), including its Innovations in Graduate Education (IGE) track, offers funding support for new testbeds for training graduate students and postdocs in interdisciplinary areas, which can serve as a mechanism for Convergence research education.155

Faculty
Convergence education also presents challenges at the faculty level, where hiring, advancement, and tenure decisions are dominated by departments organized around particular disciplines. For example, such decisions are often based on the number and quality of publications crediting a candidate as principle author. Not only do most
scientific journals focus on particular disciplines, but many prestigious journals will not credit primary authorship to multiple contributors from different scientific fields. NCI has initiated a new funding mechanism allowing staff scientists to apply for grants on their own rather than under a principal investigator, thus positioning additional scientists as principal authors, and encouraging cross-disciplinary collaboration. Faculty reward structure is only one of a series of issues in this area. The 2014 National Academies report on Convergence recommended a series of strategies for organizing convergence centers that cut across departments; changes in promotion and tenure to enable Convergence-oriented faculty; “cluster” hiring for faculty across fields; reorganization of facilities and workspaces to enable Convergence research; partnerships for Convergence research across universities and industry; and seed funding for faculty Convergence research.

Still, as described below, siloed governmental agencies and grant review practices present further hurdles to Convergence funding. Difficulty in obtaining grants leads some researchers to partner with or form companies. However, as is also the case for researchers in traditional disciplines, conflict-of-interest rules, which vary by institution, can hamper their ability to do so. There are, however, examples of organizing across agencies for education reforms. The “CoSTEM” cross-agency effort to develop a strategic plan for science education brought numerous agencies together and has developed constructive contributions in education planning. NSF’s education programs have created a home for Convergence education studies and pilot programs that are transdisciplinary.

**Government Funding Challenges**

The current administration has made great strides in supporting Convergence. The BRAIN, the Precision Medicine and Cancer Moonshot Initiatives hold tremendous promise, as do related cross-agency efforts of NIH, NSF, DARPA, DOE, FDA, and particular arms of the NIH, like the National Institute for Biomedical Imaging and Bioengineering and other institutes. NIH has the “Common Fund”—a modest research pool—for shared research across two or more of its institutes and centers. Foundations, too, support a variety of Convergence projects and institutes: Kavli, Howard Hughes, Koch, Raymond and Beverly Sackler, Burroughs Wellcome Fund, and Simons, to name a few. Nevertheless, diminished federal funding, siloed agency structures and missions, and current grant application procedures make it difficult for the Convergence Revolution to reach its full potential.

Of course, Convergence research is not only a challenge of funding levels but also of innovation organization. Convergence is a broader concept than the focus in this report on biomedical-related research. In a related field, the plant genome project in agriculture, a cross-disciplinary strategic planning process, offers a significant success story relevant here. The interagency Plant Genome 5-Year Strategic Plan is now 20 years out, in its fourth five-year plan. It has led to a broad range of technologies embodying Convergence research to improve agriculture. It suggests, in a directly relevant field to biomedical Convergence, that strategic planning across agencies, institutions, and disciplines can result in both new science and technologies, with development of supporting toolsets that can be enablers of both. While research funding issues are the focus of this section, new approaches on implementing Convergence must include science and technology strategies.

**R&D Funding**

Federal investment in R&D—including basic research, the fundamental building block for innovation and economic advancement over time—has diminished steadily as a share of the economy since the 1970s. There was also a decline in research investments by large companies, as measured, primarily, by diminishing numbers of publications in
The private sector dominates development funding and government research funding. Development over time depends on advances from research; both are required and are mutually reinforcing. Weakening one affects the other. Within this R&D total, research has been in decline with development assuming a larger share of overall R&D. But the greatest decline was due to ongoing federal budget cuts for early-stage research.165

As a result of these federal cuts (particularly through budget caps and sequestration with its decade of research cuts from 2013-2023, as well as inflationary losses), federal funding for R&D, including basic research (where government is the largest supporter) has diminished as a percent of GDP, from 1.2 percent in the late 1970s, and in the past five years from 1.0 percent in 2009 to 0.79 percent in 2014.166 Between FY2003 and 2015, the NIH, the nation’s primary funder of medical research, lost 22 percent of its capacity to fund research.167 Although Congress has raised the NIH budget by 5.9 percent for FY2016, NIH’s capacity to fund research, at just over $32 billion, is still lower than it was in 2003 in inflation-adjusted dollars. This means that less than one in five grants submitted to the NIH receives funding, leaving many equally qualified projects to languish.168, 169

Convergence Funding

Funds allocated for biomedical Convergence research are severely limited as well—in part because Convergence research overlaps the purviews of many agencies, such as NIH, NSF, or DARPA, but is the central focus of none. With no “Convergence” category for grant applications or data on whether co-principal investigators are housed in different academic departments, it is difficult to measure how much funding goes to Convergence projects.

Nevertheless, it is significant that while NIH grants to engineering and bioengineering departments increased more than fourfold between 2000 and 2014,170 this increase represents a very small fraction of a total 66,700 grants funded by the NIH in FY2014. In FY2015, only 3 percent of NIH research funding went to PIs from departments of engineering, bioengineering, physics, biophysics, and biostatistics/mathematics—compared with roughly 3 percent that went to biochemistry departments, alone.171 While this is not a perfect measure of all the NIH grants supporting Convergence research—some grants going to traditional biology focused departments could and do include Convergence research—it serves as a reasonable indicator. Additionally:

- The NIH institute most closely following a Convergence model is the National Institute of Biomedical Imaging and Bioengineering; its budget of $343.5 million in FY2016 has hovered at just 1-2 percent of the total NIH budget (currently $32 billion) since NIBIB’s inception in 2002.172
- NIH’s portion of the BRAIN and Precision Medicine Initiatives include Convergence-based research and were funded for 2016 at $150 million and $200 million respectively.173 NIH’s portion of the new Microbiome Initiative is $20 million and will also likely include Convergence research.174
- DARPA, with a 2016 enacted budget of $2.87 billion, does not specifically report on Convergence funding. Its new Biological Technologies Office (BTO), which supports biomedical-related programs, has a budget in the $200-300 million per year range although the BTO annual budgets are not reported publically.
- According to a 2015 publication,175 just 5 percent of total NSF grants awarded since 2009 went to research in such emerging life science-related Convergence areas as nano-, bio-, information, and cognitive (NBIC) technologies. In the NSF Engineering Directorate, the Chemical, Bioengineering, Environmental, and Transport Systems Division (CBET) received just $184 million in FY2016 to fund not only research in biomedical engineering and engineering healthcare, but in environmental and transportation research, as well.176
To put the $184 million funding level into some perspective: the cost of bringing a single prescription drug to market over a ten-year period is approximately $2.5 billion, with $1.098 billion of that amount going to early stage/preclinical research.177

International funding comparisons

What is more, with the internationalization of medical research, spending by other countries, particularly in Asia, threatens to erode U.S. leadership in medical R&D. In 2004, U.S. spending for medical R&D made up 57 percent of the global total. By 2014, the U.S. share of the global total had fallen to 44 percent, with Asia (led by China, Japan, South Korea, India and Singapore) increasing investment by 9.4 percent per year.178

Some of those Asian investments go directly to Convergence research or facilities. For example, the China International Nanotech Cluster in the Suzhou Industrial Park includes numerous academic laboratories and some 200 companies, at least one of which received $1 billion in funding from the Chinese government. The park's operations are jointly supported by the Ministry of National Science and Technology, the Ministry of Commerce and Jiangsu Province.179

Competitive Impact


Seven years later, in 2015, the Journal of the American Medical Association wrote that if current trends continue, China will overtake the U.S. as the global leader in medical R&D in the next ten years. Compared with the U.S., China already has a greater share of the global science and technology workforce and of patents; it is now closing the gap in published biomedical research articles, as well.180 Obviously there are questions about the comparative quality of these efforts between the countries, but the point is that the scale-up of China’s efforts toward innovation-driven growth is remarkable.

In 2012, a report was co-published by United for Medical Research and the Information Technology and Innovation Foundation. Titled “Leadership in Decline: Assessing U.S. International Competitiveness in Biomedical Research,” the report found that when it comes to government funding for pharmaceutical research, “Korea’s government provides seven times more funding as a share of GDP than does the United States, while Singapore and Taiwan provide five and three times as much, respectively. France and the United Kingdom also provide more, as shares of their economies.”181 The rest of the world is moving forward while the U.S. lingers.

Health Impact

Not only do levels of funding for early-stage and Convergence research threaten the competitive stance of American biomedical industries over time, they threaten the progress of Convergence. They also affect the work of young scientists, who are generally more oriented to Convergence, but whose research proposals are more likely than established researchers to go unfunded. But, bluntly stated, in immediate, practical terms, current funding levels for biomedical and Convergence research are too low to support timely solutions for major—and very costly—health care problems.

Taking just one example: The cost of Alzheimer’s disease treatment in the U.S. is now $150 billion per year and rising, with unpaid caregivers providing 17 billion hours of care. By 2050, total public and private costs in the U.S. for Alzheimer’s are expected to reach $1.2 trillion. Yet under current funding constraints, the National Institute of Aging (NIA), with a 2016 budget of $1.6 billion, can fund only 7 percent of the research ideas it receives. In the last several years, special “bypass budgets” have led to funding increases
specifically for Alzheimer’s research. And there is hope that the BRAIN Initiative and the War on Alzheimer’s disease (which coordinates brain disease research efforts at NIH, NSF, and DARPA) will bring greater understanding through Convergence efforts. However, while Alzheimer’s funding has been increased, the rest of NIA’s budget rose by only 4.2 percent, despite growing numbers of elders facing other diseases of aging.\textsuperscript{182}

To adapt a statement from the 2015 report “The Future Postponed: Why Declining Investment in Basic Research threatens a U.S. Innovation Deficit”: If we are serious about mitigating the human tragedy of disease and reducing the huge financial burden of caring for millions of affected individuals, then the time to escalate research investments is now.\textsuperscript{183}

\textbf{Agency Structures}

In addition to dollar levels, another challenge to Convergence funding involves the number, structure, and diverse missions of government agencies. While some agencies recognize the power and importance of Convergence research, others are organized to focus on funding for individual fields or diseases. For example, engineers are ordinarily funded through the National Science Foundation (NSF), Department of Energy (DOE) or the Department of Defense (DOD). Computer scientists are most often funded by the NSF or by DOD, which, of course, must focus primarily on defense. Medical scientists usually receive funds from the NIH. And research on a particular disease is typically funded by an institute focused on a particular disease area, such as the National Cancer Institute, the National Heart, Lung and Blood Institute, the Arthritis, Musculoskeletal and Skin Institute, the National Institute of Mental Health, the National Institute of Neurological Disorders and Stroke, and so forth. Convergence-based technologies tend to be cross-cutting and relevant to a series of disease areas. Cross-agency technology strategies—to enable a series of institutes and centers to take advantage of Convergence research advances and collaborate on optimal steps for further progress—are extremely limited.

The current administration is making important efforts to coordinate and manage several Convergence initiatives across agencies. But only a small fraction of R&D is coordinated. With new understanding of the interrelationships of diseases and environmental factors, and with increasing combinations of tools and technologies developed in converging scientific, medical and engineering disciplines, more efficient ways to cross-strategize and cross-fertilize government funding are greatly needed.

\textbf{Grant Applications}

Another challenge is that with Convergence still in its early stages, funding decisions for cross-disciplinary projects are often made by review panelists from specialized fields who might lack the expertise needed to judge the likely success or importance of a Convergence project. An application for a Convergence project might involve a materials scientist, a chemist, a mathematician, a computer scientist, and a molecular biologist. Current review panel compositions make it difficult to find all the expertise needed to review fairly each component of a Convergence proposal, leading to rejection of the entire project.\textsuperscript{184} This problem is exacerbated by the historical organization by universities of their faculties into departmentalized disciplines. Since review panels come from universities, the universities likewise have a role in assisting funding agencies to move their faculties toward Convergence expertise.

Chapter 5 sets out a series of recommendations to confront both the funding and organizational challenges summarized above for progress on Convergence.
Endnotes


125 National Heart, Lung, and Blood Institute, *NHLBI Fact Book, Chapter 4: Disease Statistics* 51 (2012).


130 J. Handelsman & J. Smith, *STEM for All* (2016).


135 Interview with Amir Nashat, April 2016.


143 Department of Education, *NCES, STEM Attrition*, Table 2, p. 18.
175 W. Bainbridge & M.C. Roco, Handbook of Science and Technology Convergence (2015).
177 Tufts University Center for the Study of Drug Development, Cost to Develop and Win Marketing Approval for a New Drug is $2.6 Billion, (November 18, 2014).
The scientific and technical advances of the last decade have brought us to a tipping point in which major medical breakthroughs stemming from the integration of the life sciences with engineering, physics, and information technology are becoming possible. This, in turn, will enable dramatic new health outcomes and address the challenges of increasing health care costs. Convergence is necessarily the next big movement in health research and innovation, but realizing the full potential of Convergence will not happen without major changes in funding support and strategic approaches at several levels.

Convergence needs a concerted national effort to achieve its full potential to supply the innovations that will give physicians and patients the diagnostics, therapies, information, and tools to live healthier lives. Given the demographics and related health care cost challenges society faces, this effort, and its promise of a healthier population, has now become crucial.

**Major Recommendation**

The National Institutes of Health is central to the future of Convergence research and its impact on health outcomes, as it is the biggest funder of biomedical research in the country. The real change needed—beyond incremental iterations within the agency—is a robust, steady and sustained boost to the NIH budget above inflationary levels. Within such increases, funding should be targeted to Convergence research, without detriment to—but rather complementing and enhancing—other research budgets. The most critical recommendation is to increase the portion of NIH support to embrace Convergence research; at least 20 percent of its research budget—implemented across its institutes and centers—should support this new research model in the reasonable future.

**Related Recommendations**

Among federal agencies, the National Science Foundation is the primary source of support for basic engineering and physical sciences, and plays a critical role in supporting the foundational Convergence fields needed for health advances, from physical and computational sciences, to basic research in mathematics, and biology, as well as important work in science education. NSF has now made Convergence, broadly defined, a major research priority, but defers to NIH on medical research. Although other federal agencies such as the Department of Energy, Defense Advanced Research Projects Agency, and the Department of Agriculture recognize the promise of Convergence, to date, no federal agency or office has the primary responsibility to promote the Convergence of engineering, physical, and mathematical sciences with biomedical sciences.

The NSF, DOE, and Department of Defense research (including DARPA) will need to continue to play a significant and growing role in advancing Convergence in a manner needed to make real changes in the near future; they will require significantly expanded funding support to do so. Finally, the Food and Drug Administration will need to make substantial changes to its review processes to facilitate the distribution of Convergence-based medical products so needed by patients. Its “regulatory science” research agenda should fully embrace and better enable Convergence approaches.

As outlined in the first chapter of this report, more and more universities and organizations are embracing Convergence research and education approaches across the country, despite the relative lack of funding for such work. Imagine the impact these groups could have on the future of health given the proper support and incentives.

In addition to robust funding increases for Convergence research, a series of more specific policy recommendations are set out below to advance the Convergence Revolution in the federal, academic, industrial, and philanthropic sectors.
Detailed Policy Recommendations

Federal

Interagency Collaboration and Efforts
While NIH leads life science research funding, other agencies have expertise and resources in physical, engineering, and computational sciences and must be involved in the Convergence effort to speed progress. As only approximately 3 percent of NIH funding went to principal investigators in bioengineering, engineering, biophysics, physics, biostatistics, and mathematics departments in FY2015, this key community is not being adequately engaged in Convergence research. The BRAIN, Cancer Moonshot, and Precision Medicine Convergence-based initiatives have recognized this need for interagency efforts. Such efforts should be expanded more broadly, and supported across agencies, as suggested below:

Funding: Because of its significant promise for health advances and its current modest scale, Convergence research funding at key agencies should be increased significantly, although not at the expense of other research funding, which would be counterproductive.

Congress should support sustained growth above inflation across the key science agencies (including at NIH, DOD, NSF, FDA, and DOE) for life science research overall; Convergence research at NIH in particular, as noted above, should rise to 20 percent of its research portfolio across its institutes and centers, with comparable overall funding increases at the other agencies.

Mechanisms should be created to allow interagency funding and research collaborations on common research issues, where shared expertise would be advantageous to conducting the research. Although interagency funding models are challenging to execute, there are mechanisms to employ the expertise of several agencies in concert to address Convergence research challenges. A few examples to emulate include:

• The National Robotics Initiative between NSF, NASA, NIH, USDA, DOD, and DOE. Each agency prepares its own solicitation for grant proposals, but the agencies act in concert to collaboratively push forward a research agenda.

• The BRAIN Initiative in which NIH, NSF, DARPA, FDA, and I-ARPA bring researchers together at collaborative PI meetings to exchange ideas across areas of expertise, although each agency funds its own grants separately.

• The Tissue Chip for Drug Screening program was essentially a technology handoff from DARPA to NIH and FDA. Program reviews for the research take place at DARPA and NIH on consecutive days to encourage cross-talk among experts.

Working Group: Create an interagency working group on Convergence with NIH, NSF, DOD, FDA and DOE participation, coordinated through the Office of Science & Technology Policy at the White House. The charter of the working group would be to identify new cross-agency Convergence initiatives and opportunities as described below. Models for the effort include the Advanced Manufacturing Partnership and the follow-on collaborative interagency project.

Researchers may lack access to instrumentation and the facilities needed for advanced Convergence research. The Working Group could also evaluate opportunities and needs for shared facilities to provide access to advanced scientific tools and trained technical support staff.

Emerging Initiatives: Use the initiative model to create more Convergence interagency collaborations, like the BRAIN and Precision Medicine Initiatives, based on promising Convergence research topics.

External Experts/Convergence Frontiers Study: Create an external advisory committee of noted researchers with Convergence expertise to advise the federal agencies about the newest frontiers of Convergence research.
Following the type of model developed by the Basic Energy Sciences Advisory Committee, conduct a far-reaching study on the next frontiers of Convergence research by convening experts from around the country to conduct multi-day workshops to identify and prioritize key emerging Convergence research opportunities. This effort should inform the Convergence research strategy approach suggested below, as well as comparable complementary strategies that could evolve at other agencies. It could also inform the selection of research areas for NIH Convergence Frontier Research Centers proposed below.

**Convergence research strategy:** The agency working group, with the advisory group, building on the Convergence Frontiers Study, as well as agency technology strategies, should develop an ongoing strategic plan for biomedical Convergence. The Plant Genome 5-Year Strategic Plan, referenced in the previous chapter, and the National Nanotechnology Initiative suggest possible models.

**Training:** Significantly expand the number of fellowships and traineeships from various agencies that specifically focus on Convergence themes for the next generation of researchers.

Expand the NSF National Research Traineeship (NRT) to include a Convergence research track, similar to the previous themes like Cyber-Innovation for Sustainability Science and Engineering (CyberSEES) in past IGERT traineeships.

**Convergence Curriculum:** Led by NSF and NIH, agencies should cooperate to encourage universities to develop courses and modules for Convergence education, adopting online and blended learning approaches.

**Peer review reform across agencies:** Although each agency has its own approach to peer-review and panel composition and recruitment, it is essential to ensure that the experts on review panels include multidisciplinary representation from engineers, computational scientists, physicists, and life scientists to review Convergence research proposals accurately.

**Higher risk research:** Encourage the award of more high-risk high-reward research, where much of Convergence research resides.

Focused efforts at particular agencies are also needed:

**National Institutes of Health (NIH)**

NIH presents a critical but challenging organization model for Convergence research. The agency is divided into 27 institutes and centers (ICs) largely organized around particular diseases; this makes introduction of research on cross-cutting new technologies that affect a range of diseases complicated—a key issue for Convergence research. NIH is also focused historically on biology, with biology-trained scientists and program managers dominating its research and workforce. This further complicates Convergence research, which relies on integration of engineering and physical science with biology. The recommended approaches below could help meet these challenges:

**Improve collaborative research across the 27 NIH institutes and centers:**

**Common Fund:** Use the Common Fund as an incentive to collaborate across ICs. “The NIH Common Fund was enacted into law by Congress through the 2006 NIH Reform Act to support cross-cutting, trans-NIH programs that require participation by at least two NIH Institutes or Centers (ICs) or would otherwise benefit from strategic planning and coordination.” Convergence research offers new technology advances that could speed progress across diseases, and closely fits the Common Fund concept.

**NIH Convergence Working Group Strategy:** Create a "Convergence Working Group" across institutes at NIH, housed in the Office of the Director, Office of Science Policy. It should include representatives from affected NIH ICs who would meet regularly to develop an overall Convergence strategy for NIH and its ICs and serve as a resource for individual ICs to more fully develop their Convergence research strategies.
Encourage the Convergence working group to develop a cross-IC Convergence research strategy and agenda, identifying promising Convergence research areas and ways NIH could exploit them. This effort should include collaboration with the interagency working group and with the external advisory committee (both noted above). The BRAIN and the Precision Medicine Initiatives provide good examples of how this strategizing can be done in particular areas, proving the model. However, there are many other promising Convergence research frontiers that also need to be addressed and should now be considered as a whole—not as isolated cases—because they share common issues.

**IC Convergence Research Agendas:** Encourage the ICs to develop their own Convergence research agendas by developing five-year strategic plans to better incorporate Convergence approaches in their missions, drawing on the findings of the above strategy, to advance their individual missions, and to recruit appropriate program officers and leadership with Convergence expertise.

**Convergence Frontier Research Centers:** Fund, through involved ICs, unique larger-scale facilities and centers at research institutions that would aid and pursue Convergence research, based on the successful model of the Energy Frontier Research Centers in key areas of Convergence research frontiers as defined by the external advisory committee in collaboration with the interagency working group (noted above).  

**Workforce Training:** Without a workforce more fluent with Convergence research, promising advances will not be realized. While NIH historically has operated on a focused biology research model, this lens needs to be broadened to include talent from other fields in engineering and physical sciences critical to Convergence-based advances.

Expand and focus a subset of the NIH T32 Training grants to train more Convergence researchers in Convergence research themes. The NIH deserves credit for creating the Biomedical Big Data track as an option in the T32 lineup. Additional Convergence-themed tracks such as this would be very beneficial to training the next generation of Convergence researchers. One example is the NIGMS Biotechnology Predoctoral Training Program, which emphasizes training in engineering and quantitative approaches to biomedicine.

**Food and Drug Administration (FDA)**

Like NIH, FDA lacks expertise in Convergence fields, which limits the ability of FDA to review new Convergence-based health technologies. FDA also has long recognized its need for better “regulatory science” to reduce the time and cost of its regulatory approvals. This improved processing will be key to the introduction of Convergence technologies and the pace of their advance. Recommendations are:

**Regulatory Science and Convergence:** Research and implement new models for “regulatory science”-based approaches to better accommodate Convergence therapies that do not fit the traditional mold of FDA approval pathways. One example may include “parallel coding” efforts in which Convergence advances are framed in the context of previously-approved products to ensure that Convergence innovations are not held back unnecessarily by FDA during the approval process simply due to novelty.

**Training:** Expand the current FDA fellowships and internships to be more inclusive and appealing to engineers and data scientists.

**Convergence Staff:** Train and hire more Convergence-fluent employees at FDA, especially to efficiently review medical devices and non-traditional Convergence therapies (beyond standard drugs).

**Realignment:** Structure FDA processes to better accommodate advanced technologies and Convergence approaches so there is a clear Convergence track to therapies.
Although NSF defers to NIH on medical research, it plays an important role in supporting the basic sciences that provide the foundation of Convergence in health—in engineering, computing, mathematics, other physical sciences and biology. NSF has recently announced Convergence as one of its new research priorities, which is a significant step for the Convergence overall, including in health. In addition to broad Convergence research, NSF also has a central role in science education, where it can provide significant support for new education models. Numerous recommendations above include NSF; to summarize, these include: the need for additional research support for Convergence work at NSF and for NSF overall at a level that sustains growth above inflation; NSF participation in a new cross agency working group to design new Convergence health strategies; interagency research collaborations where NSF should play a significant role around new Convergence initiatives (which will require additional funding), such as the BRAIN initiative, in which it already participates; expansion of shared Convergence instrumentation facilities for university research; expansion of NSF’s National Research Traineeships to include a Convergence track; and development at NSF of Convergence education curricula.

There are other roles in Convergence that NSF has under consideration that we believe could be quite significant:

**Education:** develop a new “culture of Convergence” that better links physicists, engineers, data scientists, mathematicians, biologists and other fields, and embody this in science education research and new directions for teaching and education.

**Convergence Research:** research support at NSF has encouraged Convergence advances, such as an artificial retina and development of synthetic biology, tissue engineering, and metagenomics. Its Convergence research portfolio should be expanded, as it is now a stated goal of the NSF.

**Peer Review:** restructure the review process and timeline for proposal awards at NSF to foster Convergence research.

**Engineering Research Centers (ERCs):** NSF-sponsored ERCs bring together universities and industry for common R&D efforts; work at these is already having a Convergence impact, such as supporting the field of robotic surgery. Additional focus at ERCs on Convergence topics and goals offers a promising applied research and translational model for Convergence.

**NSF Common Fund:** development of an NSF version of NIH’s “Common Fund” could be a new tool promote cross-cutting science across its Divisions in broad Convergence fields.

**Defense Advanced Research Agency (DARPA)**

DARPA is now playing a critical role in the development of Convergence in health, recently solidified through its new Biological Technologies Office. Its work on health research will naturally focus on areas of need for military personnel and defense. But that work includes sponsoring frontier research in such areas as brain function and disorders, infectious disease, synthetic biology, rapid prototyping and production of drugs and therapeutics, organ and system modeling and simulation, and bio threats. While DARPA undertakes research to solve challenges, the net result has been a pursuit of breakthroughs involving the Convergence research model. DARPA has also been willing to partner with other agencies where it is advantageous for both, such as in the BRAIN initiative and through its shared project with NIH on the “Tissue Chip for Drug Screening.” DARPA’s Convergence research using its “challenge” model should continue to grow. DARPA has a unique research approach with a long history of breakthrough results which move rapidly into implementation. Its often pioneering work at the frontiers of research and technology can continue to contribute to major advances through Convergence in health areas that fit its mission.
National Academies of Sciences, Engineering and Medicine
The Academies, through the National Research Council, has provided important support in recent years for Convergence through important studies, workshops and a major new Convergence prize in collaboration with the Sackler Foundation. This important work should continue and the Academies should evaluate agency progress in implementing Convergence along the lines recommended here as well as periodically assess evolving opportunities where Convergence-based research could make important progress.

Academia and Higher Education
Although many innovative programs have been developed at universities across the country (see examples in Chapter 1), there is still much academic inertia to overcome before Convergence research advances can be fully realized. The traditional structure of siloed disciplinary-based departments is still the norm and it is often hard for Convergence-thinking researchers, faculty, and students to break out of the confines of such barriers. Although the importance of deep disciplinary expertise must be acknowledged, Convergence thinking and corresponding training is essential to solving thorny problems in health. While some aspects of departmental structures at universities must be retained, finding a balance of Convergence approaches across disciplinary siloes could catalyze health solutions. Recommendations include:

Education: Educate the next generation of Convergence researchers:
• Use online education resources to provide Convergence training in statistics, computation, and big data analysis that is accessible to all students, regardless of location, and develop Convergence courses and modules in online and blended models to scale up this training.
• Introduce better statistical and programming education for students. Every student needs a common foundation in computational science and statistics.
• Excite students by giving them problems to solve, rather than additional disciplines to join.
• Create flexible advising models so that students feel less beholden to a single department at a university and have more flexible access to others.
• Establish “one-of-a-kind” Ph.D. programs in which students working with their faculty advisors design their own degree programs across disciplinary boundaries to foster Convergent doctoral training.

Hiring and Tenure: Update hiring and tenure practices to be more welcoming to Convergence researchers.
• Allow for cross-department hiring.
• Encourage cross-department tenure review.
• Consider interdisciplinary, non-single author publications as equal to single-author publications in tenure review.
• Consider “cluster” hiring across disciplinary fields relevant to Convergence.

Space: Provide more convening spaces to mix biologists with engineers, data scientists, and physicists.
• Encourage cultural exchanges among disciplines, as in informal cross-discipline research talks, etc.

Seed Funding: Provide seed funding for Convergence teams and projects to develop Convergence research projects and proposals.
Career Grants: Enable faculty to support ongoing Convergence efforts in both their own careers and for their trainees. Options may include:

- **Endowed Convergence Department Chairs**: The significant cost to recruit and keep faculty skilled in both a robust understanding of multiple disciplines and the capability to work across them should be supported through endowed chairs at universities across the country.

- **Convergence Research Support**: Funded Convergence Sabbatical opportunities for mid-career faculty should include the opportunity to take some significant portion of time away from current research to return to the university to study an alternate and related field of study. This “staybatical” approach is exemplified by the Mellon Foundation’s New Directions program.¹⁹⁴

**Philanthropy**

The philanthropic community has made great contributions to Convergence research by catalyzing the creation of new programs, supporting innovative convergent researchers, and advancing the discussion on barriers and solutions to Convergence progress. There is tremendous potential for private funders to continue advancing the Convergence agenda and defining new frontiers in Convergence research, such as:

**Fellowships**: Expand Convergence research fellowships for graduate students and post-docs.

**Public-Private Partnerships**: Catalyze the initiation of more national initiatives like the BRAIN initiative through public-private partnerships.

**Research Agenda**: Convene stakeholders from across the country to expand on the Convergence research agenda. (Which areas of research are most ripe for advancement, but perhaps too underdeveloped for federal investment?)

**Centers and Institutions**: Fund Convergence research and training centers and institutions at universities and across universities.

**Industry**

The industrial sector is embracing Convergence at a remarkable pace. This sector naturally embraces a Convergence approach because it is driven by real-world problems and market needs, which require multi-disciplinary skills and broadly educated teams. Because industry relies so heavily on a workforce educated through academia and its research systems, recommendations include:

**Hiring**: Change hiring practices to incentivize the development of a workforce with Convergence skills. Provide incentives for employees to interact with training programs to provide encouragement and advice to students trained in Convergence.

**Workforce Training**: Enhance collaboration at every point of the innovation supply chain to encourage the Convergence skills needed in industry now and in the future.

**Partnerships**:

- Build academy-industry relationships to foster opportunities in pre-competitive space.

- Strengthen ties between industry and academe to invest in intellectual property and sponsor research.

- Encourage local or state governments, industry organizations, community colleges and high schools to provide training for work in convergent fields, especially in computer and IT skills.

**Funding**:

- Fund earlier stages of R&D by participation in pre-competitive research in important Convergence fields.

- Join with foundations to fund discovery competitions for universities and researchers.
Endnotes


186 National Institutes of Health, “NIH funds next phase of Tissue Chip for Drug Screening program”; (2014); and Massachusetts Institute of Technology, “DARPA and NIH to fund ‘human body on a chip’ research” (2012).


191 National Institute of General Medical Sciences, Biotechnology Predoctoral Training Program (2014).


