CHAPTER 5

IMPLICATIONS: HUMAN HEALTH AND PHYSICAL POTENTIAL

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Societies all over the world benefit from medical advances made possible by the interplay of science and technology. Seldom are these advances simply the straightforward result of traditional improvements in manufacturing or automation or increases in scale. Instead, these improvements emanate in large part from the application of newly developing knowledge towards solving technological challenges. Convergence is the next-generation iteration of that process, resulting in new solutions and enhanced return on investment. This chapter deals with the role of convergence and its application in advancing health and wellness for the world.

5.1 VISION

5.1.1 Changes in the Vision over the Past Decade

The pre-convergence process in science and technology advancements was dependent on coincidence (“passive convergence”). In fact, many of today’s keystone medical tools were derived by happenstance, and their histories often illustrate the fundamentals of progress in action (as illustrated in section 5.2.1).

Organizational models have played an important role in the probability of productive convergence. Highly productive and innovative organizations like Bell Labs, Genentech, Hewlett Packard (leading to Agilent), and MIT’s Media Lab tend to share a few common characteristics. The first is a collection of highly accomplished experts gathered from a range of only marginally related fields. The second is an operational and cultural “openness” to considering what could be possible or impactful. The third is a determined group-based drive and expectation to deliver revolutionary rather than incremental outcomes. Transforming medicine and human potential will depend on these types of attributes, and much can be learned from organizations that operate on these principles.

5.1.2 The Vision for the Next Decade

The practice of medicine is moving from a passive coincidence model to an active convergence model. At the center of this transformation is the intersection of physiology, molecular profiling, and information technology. Today’s hallmarks of wellness and disease have their origin in measurements of vital signs such as pulse, temperature, blood pressure, and respiration, each with its specific method of measurement. The vital signs of tomorrow will be based on concentrations of molecular analytes detected in various body fluids and in exhaled breath and will be measured using minimally invasive imaging or on-body sensors. The resulting molecular profiles, often simultaneously measured via multiplexed interrogation of numerous analytes, will more precisely distinguish wellness from a disease state, efficacy from toxicity, and regression from progression.

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This form of “precision medicine” is centered on the consideration of the individual, is deeply reliant on a molecular understanding of a disease, and is coupled with emerging analytical tools competent in measuring the resulting biochemistries (NRC 2011). We expect that these new models will improve the health of patients by transforming medicine from a reactive into a proactive practice and result in efficiencies that reduce the overall cost of healthcare (Figure 5.1).

![Figure 5.1](image-url)  
**Figure 5.1** Worldwide economic impact of treating different diseases (O’Callaghan 2011; ©Nature Publishing Group 2011; permission to reuse through Rightslink).

### 5.2 ADVANCES IN THE LAST DECADE AND CURRENT STATUS

#### 5.2.1 Advances in Converging Technologies

Coincidence in medical advances of the past was a dominant trend. Blood pressure measurement (sphygmomanometry), fundamental to the field of cardiology, is an example. It primarily began with Stephen Hales, who in 1773 proved that the mammalian circulatory system operates on the basis of pressure when reporting his observation, “that by attaching a long length of glass capillary tubing to the artery of horse, the blood rose in the tube 8 feet and 3 inches perpendicular above the level of the left ventricle of the heart” (Booth 1977). It took until the middle of the 19th century for the physician-physicist Jean Louis Marie Poiseuille to further advance the field by inventing the mercury-based manometer. This instrument enabled accurate arterial pressure measurements for the first time. But his instrument and those noninvasive instruments that followed are only half of the story. Considered a “vital sign,” blood pressure measurement has proven invaluable in the clinical management of trauma. However, it is its use in detecting hypertension that it resulted in saving millions of lives.

In the late 1800s, the astute pathologist Rudolf Virchow first reported his observation of arterial occlusion (Caplan 2000) to be coincident with hypertension. Subsequent chemical analysis of these occluding substances—yellow lipid-like materials—revealed their principle component to be a molecule termed “cholesterol.” Over the ensuing decades of the twentieth century, the cholesterol biosynthetic pathways were characterized and critical enzymes were identified, with HMG-CoA reductase being particularly interesting, because it was druggable with statins. In the 1970s the first clinical trials of statins began, and after a few starts and stops associated with ensuring safety and efficacy, the widespread use of these drugs in patients with elevated blood lipid levels has translated into a tremendous reduction in cardiovascular system-associated death and morbidity (Tobert 2003). Cardiovascular system-associated deaths per 100,000 in the United States have dropped from ~600 in the 1950s to ~200 today (Figure 5.2); similar dramatic reductions have been seen everywhere these medicines are given.
When invented, the tools to measure blood pressure were designed to help us understand physiology and the mechanics of how our bodies worked, but unexpected extrapolation and convergence resulted. The subsequent linkage of coronary occlusion, lipid metabolism, and hypertension (i.e., high blood pressure) would have been impossible to predict, yet their role in health or disease is indelible and illustrative. The development of a reliable and accurate analytical method (sphygmomanometry) by experts in one field and its deployment in measuring a disease process by experts in a completely different field (primary care and/or cardiology) developed by coincidence. Events and individuals separated in time and space were connected through sharing of information and the development and dissemination of analytical methods.

Medicine today is supported by a dizzying array of tests. Detailed molecular testing began in earnest with blood transfusions, followed by its use in tissue transplantation in which “testing” patients to find those with sufficiently similar “types” was a fundamental requirement for treatment success (Murray and Holden 1954). These precursor tests were soon followed by a tsunami of diverse medical tests to catalog and index a remarkable number of analytes and/or anatomical details, with some now serving to confirm wellness while others are used to screen for evidence of disease.

Convergence is a primary driver in this aspect of medicine. In recent years, especially given advances resulting from the effort to map the human genome, the potential for new tests have emerged that can accurately predict the efficacy of certain medicines and the potential toxicities among subsets of the population corresponding to distinct genetic markers. While there is still much work to do, many medicines in the regulatory approval process today are co-developed with tests that strive to define the optimal patient population (Hamburg and Collins 2010). In many cases these therapies for targeted populations represent only a small fraction of the total patient pool, but in these precise subsets, profound benefits of treatment are apparent.

In addition to this new era of medicine, patients and their physicians today are presented with remarkable, albeit in many cases overwhelming and disjointed, amounts of medical information. Driving much of this are information systems and hand-held devices that are now ubiquitous agents in society. In medicine, these resources are changing the relationships between symptoms and diagnosis and doctor and patient. Concurrent with these changes in information systems and related access is a rapid change in the physical form of the medical record itself. Rapidly vanishing are the individualized paper-based medical records of the past. These are being replaced with electronic medical filing systems connected to networks. While standardization and interoperability are still
challenging issues, a primary goal of this effort is to learn more about modeling health for populations by sharing instantly the results collected in one medical setting with other medical professionals and then comparing results with millions of anonymous patient files with similar attributes (Grossman, Powers, and McGinnis 2011).

5.3 GOALS FOR THE NEXT DECADE

Given the advances over last 10 years, the practice of medicine will change in remarkable ways over the next decade, and convergence, along with mounting economic pressures, will drive many of these changes. It is clear that a focus on a few targeted advances could have broad catalytic implications for healthcare. These actionable goals are outlined below.

5.3.1 Goal 1: Advance Cancer Detection and Treatment with Reduced Side Effects

Why, why now, what are the strategy and the drivers?

Since its earliest descriptions, the experience and the treatment of cancer have been synonymous with suffering. Although new treatments are being developed, improvement in reducing disease-associated death has been slow (Figure 5.2). As we have learned, the ability to detect aggressive cancers “early,” meaning before they have metastasized and so can be removed surgically, is the most effective method of achieving treatment success. However, identifying reliable and predictive markers of disease has been difficult. The first major success was derived from the work of George Papanicolaou who in the 1920s reported observations of “abnormal cells” derived from cervical scraping, but it was not until the 1950s that the “Pap Smear” began to make its way into standard of care (Elgert and Gill 2009). When coupled with a minimally invasive surgical technique, this early detection and subsequent treatment has dramatically reduced death and morbidity associated with cervical cancer. Mammography, colonoscopy, and various blood tests are important contributors in detecting cancers early, but minimally invasive approaches that can clearly differentiate aggressive from benign tumors, or metastatic from pre-metastatic lesions, are generally lacking.

The early successes in diagnosing and treating some cancers unfortunately do not translate to all types of cancer. Figure 5.3 shows typical time of disease diagnosis for prostate, ovarian, lung, and pancreatic cancers. It is clear that the majority of pancreatic cancers are both aggressive and diagnosed very late. This combination means that less than 10% of diagnosed cases qualify for surgery—the only path to a lasting cure—and the resulting 5-year survival rate is less than 15% (Goetz 2008). Significant improvements in detecting early stage disease are anticipated as the human proteome is more deeply explored over the next decade and panels of biomarkers emerge that can provide increasingly detailed diagnostic guidance. Implementation of these diagnostic assays into clinical tools will rely on the convergence of analytical tools, mathematical and computational approaches, surface and materials chemistry and engineering, and nanotechnology-based imaging and measuring tools.

Cancer treatments typically involve a combination of surgery, chemotherapy, and radiation therapy. The collateral toxicity of such treatments and the tendency of certain tumors to develop a resistance to chemotherapy are often primary constraints in achieving meaningful remission. New improvements related to the use of nanoparticle-based drug delivery (Figure 5.4) may provide new solutions (Ferrari 2005; Sinha et al. 2006; Wang, Langer, and Farokhzad 2012). Most of the recent developments in nanotherapeutics are focused on delivery of existing, already-FDA-approved chemotherapeutics (Farrell, Alper, et al. 2010; Farrell, Ptak, et al. 2011).
Figure 5.3 Time of diagnosis for different types of cancer varies with advancement (stage) of disease (Goetz 2008; © Wired Condé Nast 2009, used by permission).

Figure 5.4 Multifunctional nanotechnology-based drug delivery systems (Sinha et al. 2006; ©Molecular Cancer Therapeutics, permission to reuse from RightsLink).

Nantherapeutic formulations of these existing drugs can yield multiple advantages. First, nanoparticle circulation times can be made to be many times longer than small molecules, and so the nanoparticles have more time to find the tumor before they are passed from the body. Second, surfaces of nanoparticles can be modified to recognize the tumor, thus increasing retention time near the diseased site (Hrkach et al. 2012). Third, a single nanoparticle may hold a thousand or more copies of the drug molecule. The net result is that the drug is selectively delivered to the
tumor at a high dose, while the overall amount of drug that is given to the patient is dramatically reduced. The potential, which is already being realized for certain cancers (Heath and Davis 2008), is to maximize the tumor-killing capacity of the drug while minimizing the toxic side effects of that drug, with the goal of quickly and fully removing the tumor before it evolves a resistance to the therapy (Yoo et al. 2011).

The resulting design modifications of nanocarriers will lead to further improvement of therapeutic effect through endocytosis-mediated uptake of nanoparticles to bypass efflux pump mechanisms of multidrug resistance (Farrell, Alper, et al. 2010; Farrell, Ptak, et al. 2011). The goal of these improvements in treatment selectivity, as well as patient stratification, is cancer therapies with no side effects. If these advances are made in cancer treatment, they will have parallel and high-impact contributions in many other medical conditions as well.

5.3.2 Goal 2: Improve Health Data Analysis and Delivery for Real-Time Health Monitoring Towards Wellness

Why, why now, what are the strategy and the drivers?

Today in medicine the average consumer depends on the internet, physician, and pharmacist for regular health monitoring and maintenance. However, a new kind of wellness opportunity is emerging through the use of digital health aids. This includes the introduction of a new stage of in-home or on-body medical and monitoring sensors coupled with medical expertise, as well as treatment distribution and information systems. At an early stage, such aids may act like health coaches, as integrated systems capable of providing dynamic feedback as well as appropriate or corrective action to support personalized wellness regimes. Versions of these aids already exist in the “app” world for smart phones. While these are useful as monitoring partners for goals that include exercise, weight loss, and medication regimes, the apps still for the large part depend on the information the user manually enters.

Moving forward, the convergence for medical information technologies poses unique opportunities to advance human wellness on an automated level. For example, smart homes, originally conceived as a way to provide convenience, improve security, and save energy, are now increasingly envisioned as a means to improve the quality of life for individuals with disabilities or decreased function due to aging (Ding et al. 2011; Chan et al. 2009).

Potential functions in smart homes include health monitoring, assistance with daily living activities, and illness and injury prevention. Relevant technologies might include interactive displays or video communication with caregivers to provide reminders of daily schedules, tracking of medication usage and physical therapy needs, care and even feeding of pets, and smart appliance reminders when staples such as milk or bread are getting low. GPS technologies can be used for small tasks like tracking the location of eyeglasses, e-readers, or house keys, or more aggressively for potentially tracking the location of an individual with mild dementia and even triggering interactions with caregivers or emergency personnel.

A key factor in the effectiveness of eHealth/telehome-care lies in the design of human-network connections that can be personalized and specialized to the needs, privacy requirements, and habits of the user (Kadouche et al. 2009). Figure 5.5 outlines the factors included in developing such an in-home monitoring approach. These home monitoring technologies are not only useful in cases of monitoring the health and wellbeing of individuals at risk in the home. Such system technologies could also enable a new understanding of the interactions between wellness and the “exposome,” or the impact on health outcomes of an individual’s or even of a community’s environment over time.
This potential contribution of smart monitoring to understanding the contributions of exposomes to wellness and disease is evidenced in a recent NAS report, which calls for the development of an "Information Commons and Knowledge Network" to measure patient outcomes over time using the phenotypic and molecular data on individual patients, and including information about social and physical environments: "[D]ata added to the Information Commons should not be limited to molecular parameters as they are currently understood: patient-related data on environmental,
behavioral, and socioeconomic factors will need to be considered as well in a thorough description of disease features” (NRC 2011, 37). The goal of this effort is not only to maximize treatments for individual patients, but also to develop a new taxonomy of disease using the macro-level data gathered to better understand health trends in populations.

The effort to understand health at the macro level is reflected in a companion effort to gain a better understanding of health at the cellular level. In both cases, the eventual goal is to provide automated digital responses that do not depend on manual data entry, but on the behavior and biology of the user. For instance, the National Science Foundation Science and Technology Center Integrative Partnerships program called EBICS (the Emergent Behaviors of Integrated Cellular Systems) is led and managed through a partnership between multiple universities and hospitals. Among a long list of EBICS projects is an effort related to diabetes, to create an injected biosensor that can detect the level of glucose in the body and provide the readout visible on the skin using fluorescent markers. This kind of biomachine would lessen the pain of monitoring experienced by diabetes patients, and increase overall health outcomes.

As described above, the development of next-generation digital system aids that will function both outside and within the patient will take into account all possible levels of data and will significantly change the way we “participate” in the healthcare system. Of course, as with all scientific developments that change the way we work and function, the ethical, legal and social implications should be investigated along the way.

5.3.3 Goal 3: Promote Regenerative Medicine and Advanced Prosthetics, a Revolution in Treatment

Why, why now, what are the strategy and the drivers?

In the 20\textsuperscript{th} century medicine was changed forever by the discovery and dissemination of antibiotics and vaccines. Injuries and infections that would have otherwise proven to be maiming or fatal were shown to be treatable or even preventable. Moving forward, the hallmarks of the 21\textsuperscript{st} century’s transformative moments in medicine will likely involve tissue regeneration and repair. Many of our most grand medical challenges arise at the level of tissue dysfunction. Some of these are the result of trauma, while others are the result of genetic abnormalities or degenerative processes. To regain or restore function requires introducing cells with regenerative capacity or transplanting preformed tissue structures, or in some cases, medical devices like pacemakers, whole joints, and prosthetics.

The art and science of tissue transplantation has made tremendous progress since its origins in the 1950s; millions of people are alive today as result of artificial organ therapy (Khademhosseini, Vacanti, and Langer 2009). Advanced surgical techniques coupled with immunosuppressive drug regimens have continued to push survival rates higher; yet access to transplantable tissues remains sharply below demand. Over 110,000 Americans are on the lists for organ replacement, and more than 87,000 of these patients need kidneys. But only about 17,000 Americans get kidneys each year, while several die waiting. Increasing the percentage of organs that are available for donation would be an important contribution, but progress is also well underway to “manufacture” patient-specific fully functioning tissues and organs in the laboratory.

In simple terms, regenerative medicine can be grouped into three functional categories:

1. Replacement, which reflects mechanical exchange
2. Repair, which typically uses exogenous cells added to damaged tissues
3. Regeneration, which relies on the mobilization of endogenous pools of stem cells

\footnote{Membership includes Massachusetts Institute of Technology (lead), Georgia Institute of Technology, University of Illinois at Urbana-Champaign, City College of New York, Morehouse College, University of California-Merced, Brigham and Women’s Hospital, Emory University, Princeton University, Tufts University, and University of Georgia.}
Progress toward “making” patient-specific tissues will be driven by advances in autologous stem cell biology and advanced material sciences—a convergence of “replacement” and “repair”.

The subject of daily media attention and endless controversy, stem cells have the remarkable ability to differentiate into diverse cell types and are the precursors of all the tissues in our bodies. During development, each tissue builds its own custom scaffolding from materials called the extracellular matrix (ECM). Recently, it has been discovered that stem cells “read” these 3D architectures and microenvironments to determine which differentiation program to activate. This new understanding opens the door for a convergence of biological engineering and nanotechnology. Using 3D nanoprinting technologies, work is underway to create tissue-specific structures out of ECM onto which patient-derived stem cells can be seeded. Once those cells are fully encased and differentiated, whole and autologous replacement organs or structures can be potentially realized.

With these advances, one can imagine “curing” diabetes by replacing a compromised pancreas, as could other diseases’ negative impact be lessened by replacing organs such as the heart, liver, or kidney with a custom-manufactured version, which would remove the days of waiting (or dying) on organ transplant lists. A greater understanding of how to compensate for compromised organs would also lessen issues associated with organ rejection.

These interventions may seem costly on a per-patient basis; however, they would counter the current cumulative cost of chronic disease treatment, in addition to the loss of economic productivity while patients are disabled by organ under function or failure. A focused “convergence push” in regenerative medicine over the next decade could deliver these important medical advances and set the stage for an earlier interventional and regenerative medicine of the future, a medicine in which endogenous regenerative cellular capacities are “evoked” in patients before late-stage tissue failure predominates.

Related to biologically based regenerative medicine is the field of advanced prosthetics. Using advanced actuators, sensors, lightweight materials, and power systems, the field of limb prosthetics is making great strides toward achieving the goal of producing a prosthetic that would be so human-like that a patient or an observer could not tell the difference from an actual human limb. The march toward highly effective brain–prosthetic interfaces for brain–prosthetic communication and the fuller understanding of brain processing of information is also occurring. The current limit in neural control of prosthetics lies not within the limb itself, but in the brain—in our incomplete understanding of not only how to get signals out but how to send them. Monitoring signals from the brain with EEG, MEG, and fMRI has progressed at surprising rates, with great progress in interpreting these signals also progressing well. It is expected that we will be able to reduce to practice the interpretation of brain signals (output) using sensors placed either in the brain or on the skull, and to develop successful signal (input) interfaces.

5.3.4 Goal 4: Harness the Human Immune System as a Steady-State Monitor of Health and Disease and Tool for Next-Generation Vaccines

Why, why now, what are the strategy and the drivers?

It is hard to overstate the importance of the immune system. It plays key roles in infection, cancer, and autoimmune disease, conditions that together account each year for a quarter of deaths in the United States (Murphy, Xu, and Kochanek 2012). It is also responsible for the protective effects of vaccines, which, aside from the provision of clean water and good nutrition, constitute the single most effective public health measure in history (Rosen 1993).

It is also hard to overstate the immune system’s complexity. It comprises numerous cell subsets—including B cells, which make antibodies, and T cells, which destroy virus-infected and cancerous cells—as well as a host of molecular players. The cast of characters involved has grown as researchers have sought to define immune cells and molecules in ever greater detail. While cell subsets were once defined by microscopic appearance alone—lymphocytes are small and stain
blue; neutrophils have lobed nuclei—today they are defined by the degree to which they express specific markers, such as the cell-surface protein CD4, which is present on the surface of cells infected by HIV. Hundreds of such cell-surface and intracellular markers, as well as scores of secreted proteins like perforin and the cytokines, are now known. While there are patterns to the expression of all these markers, the number of biologically meaningful subsets they define is large and growing.

Still greater complexity is to be found among antibodies and T-cell receptors (TCRs), of which the average person has not hundreds but tens of millions of different types or “clones” (Arnaout et al. 2011; Warren et al. 2011). Different clones bind different antigens, allowing the immune system to recognize, destroy, and remember innumerable potential threats like bacteria, viruses, and cancer cells. However, these protective abilities also pressure infectious agents and cancer cells to evolve away from immune control, resulting in an evolutionary “arms race” and dynamic equilibrium in which new clones are constantly replacing each other.

Amid the complexity of antibodies and TCRs, specificity is the key: when antibodies and T cells miss their marks, they can cause autoimmune diseases like Type I diabetes and lupus, transfusion reactions, and organ-transplant rejection. But when they identify their targets properly, the immune system’s capacity to remember—so-called immunological memory—is what makes vaccination possible. Vaccines contain antigens that stimulate specific subsets of B and T cells to divide and expand in number. In this way, when the body is later re-exposed to these or similar antigens through infection or the development of cancer, it has sufficient antibodies and T cells to neutralize these threats before illness sets in.

Monitoring vaccine responses is an indispensable measure of efficacy. In practical terms, the ability to monitor the immune system is largely a matter of being able to count how many cells there are of a given subset, and to measure the concentration of secreted immune biomarkers, in the blood and in different tissues.

The way we count cells and measure concentrations today is the product of convergence among a number of 20th century technologies, including microscopy, biochemistry, genetics, tissue culture, animal models, flow cytometry, and monoclonal antibody technology (itself a product of immunology research). The convergence of multi-channel flow cytometry and monoclonal antibody technology—the ability to make monoclonal antibodies against almost any molecule, including cell-surface markers—has been especially important because it has made it possible to count thousands of cells of various subsets at a time. In fact, in hospitals around the world, the most frequently performed immune monitoring tests—the white blood cell count and differential—are performed by flow cytometry, and diagnosis of leukemia and lymphoma is made using a combination of monoclonal antibody staining and flow cytometry (in conjunction with old-fashioned microscopy). Before these technologies, diagnoses related to the immune system depended mainly on physical signs such as fever, redness, swelling, pus, and phlegm.

Despite this progress, today our ability to monitor the immune system remains crude. Only a handful of different biomarkers can be detected simultaneously using most flow cytometers, and these machines remain expensive to buy and maintain. In addition, until recently there has been no way to monitor antibodies and TCRs in all their complexity. Combined with the inherent inertial conservatism of medicine, these factors have limited our clinical capability. Fortunately, a new convergence of technologies is now transforming immune monitoring technologies, with direct implications for vaccine development, in two ways.

First, microfluidics and microfabrication techniques are making it possible to monitor and perform experiments on single cells, hundreds at a time. This represents an important advantage over flow cytometry. For example, whereas a flow cytometer can count the number of B cells of a specific subset in a sample, microfluidics makes it possible to observe how each of many cells responds to a specific controlled stimulus, such as exposure to a potential vaccine or a sequence of such stimuli over time. Meanwhile, microarrays printed with vaccine antigens can be used to quantitate a
person’s antibody responses to each antigen. Both technologies require imaging and computing. Together, they offer high-resolution pictures of what different populations of cells are up to and what they can be expected to do in particular situations, with enough fine-graining to detect both new subpopulations and stochastic behaviors that might affect overall responses. Microarrays can routinely be printed with many thousands of different analytes, and microfluidic devices can be built that allow more-or-less independent control over hundreds or thousands of individual reaction chambers, with the limiting factor being the complexity of the control circuitry.

Second, so-called high-throughput sequencing is making it possible to count and describe the tens of millions of different B and T cell clones that may be present in a given biological sample. The antigen-binding specificity of each clone depends on the DNA sequence of its antibody or TCR genes. Unlike other genes, antibody and TCR genes are generated anew in each new B or T cell, which is what accounts for the extraordinary number of clones. Deep sequencing makes it possible to monitor or “profile” the immune system by providing a readout of which clones are present in a particular biological setting, such as during infection or exposure to a vaccine. Today it is routine to sequence hundreds of thousands or millions of clones in a single sequencing run. This represents a thousand-fold increase over the number of clones that could be sequenced in a single run in the years before next-generation sequencing was introduced in 2005. For years, low-throughput studies (with sample sizes measured in the dozens or hundreds of clones) had hinted that some infections and autoimmune conditions may have “immune signatures” defined by the presence of specific sets of clones (Arnaout 2005). While the existence of such signatures remains under debate, there is considerable excitement that deep sequencing can uncover them.

Outcomes of convergence

Research interest and output in immunology and vaccines has been growing steadily and rapidly for two decades, even as other medical fields have plateaued (Figure 5.6). This growth has coincided with the birth and expansion of the therapeutic monoclonal antibody industry. The U.S. Food and Drug Administration (FDA) approved the first therapeutic monoclonal antibody in 1986. By 2010, this group of drugs, which includes rituximab (Rituxan®) for cancer and infliximab (Remicade®) for autoimmune diseases, had become the best-selling class of biologic drugs, with U.S. sales of close to $20 billion on back-to-back annual growth rates of nearly 10 percent, accounting for a third of all biologics sales (Aggarwal 2011). With $10 billion pledged by the Bill and Melinda Gates Foundation, vaccines, including cancer vaccines (Davis and Dayoub 2011), are generating similar excitement (Rappuoli, Black, and Lambert 2011). By allowing functional characterization of single immune cells, microfluidic and microfabrication technologies will contribute to vaccine development by offering precise readouts (Han et al. 2012) of the effects of potential vaccines.

Looking ahead

In the decade since completion of the draft human genome, the combination of microarray-based genotyping and high-throughput sequencing have transformed knowledge about how genes contribute to disease. It made it possible to map genetic diversity on a global scale and offered the first large-scale data to test hypotheses about how genetic differences correlate with phenotypic differences. That the correlations are not yet clear is less important than that hypotheses are now enriched by data. These advances make it safe to predict a similar transformation in immune monitoring, despite foreseeable obstacles. For example, high-throughput sequencing of B and T cells is about to receive a significant boost as key obstacles are surmounted.

The key to high-throughput sequencing is parallelism. Life Technologies’ 454, ABI Solid, and Ion Torrent platforms, and Illumina’s Genome Analyzer all achieve their throughput by sequencing many millions of DNA molecules in parallel. Read length—the amount of sequence obtained from each molecule—is generally short, on the order of a few hundred bases. Short reads have been sufficient for genome resequencing and de novo genome assembly, the applications that have driven development of these technologies so far.
But antibody and TCR genes present special challenges. Like most genes, they are longer than the read length of most sequencing platforms, but unlike most genes, they are generated through a combinatorial mix-and-match mechanism involving dozens of gene segments, and differ from cell to cell. These factors make them hard to assemble from short reads. In addition, the number of clones in a biological sample may be too close to the number of reads for in-depth coverage. (As a yardstick, the amount of sequence in a million clones is equivalent to a quarter of the human genome.) Thus, the current challenge to sequencing antibody and TCR genes is that they are too long for short-read sequencers and too many for longer-read sequencers. As a result, to date, high-throughput immune profiling studies have had to focus on particular regions within the genes—for example the third antigen complementarity-determining region of the antibody heavy chain gene—and ignored the rest. However, this obstacle should disappear as early as 2013, as increases in read length and volume across the high-throughput platforms commoditize immune sequencing by making it possible to sequence whole genes in single reads for all the clones in a biological sample.

Attention will likely turn subsequently to association studies. Over a decade ago, the development of microarrays for detecting single-nucleotide polymorphisms (SNPs) across the genome led to genome-wide association studies for diabetes risk, heart disease, and numerous other conditions.
Related technologies led to searches for, and analyses of, gene expression signatures. Whole-genome sequencing is producing ever more detailed views of different cancers and of infectious agents like *E. coli* (Rasko et al. 2011) and HIV (Tsibris et al. 2009). In the same way, immune monitoring technologies will soon be used to look for immune profiling signatures across numerous conditions and states of health. A likely focus will be chronic conditions, including chronic infections such as HIV, which has already been the topic of immune profiling studies (Scheid et al. 2011), but also autoimmune diseases, cancer, and non-disease states such as pregnancy, transplantation, and aging. In vaccine development, immune profiling will allow researchers to more easily identify and synthesize sets of antibodies and TCRs that are produced in response to antigen exposures (Cheung et al. 2012). The common goal of all these studies is predictive sequence-to-specificity mapping between antigens and the antibodies and TCRs that bind them. Such an understanding will make it possible to detect and design immune-based therapeutics for a wide range of conditions, including cancer immunotherapeutics (Fox et al. 2011)—or else reveal the fatal flaws of such a dream. At the same time, microfluidics and microarrays will provide windows into the cellular and soluble context of immune responses.

Even as association studies become technically feasible and affordable, obstacles regarding sampling and analysis will have to be overcome. One obstacle is determining to what extent, and in what situations, clones in different anatomic compartments reflect phenotypes of interest. For example, subsets of B and T cells circulate in the blood but are “home” to various tissues, including sites of inflammation, infection, and cancer. How well a blood sample will reflect these other sites is still unknown; it is a potentially important issue for monitoring or other applications that require frequent sampling. A second obstacle is to understand which subsets in a given compartment to analyze. There are also obstacles when it comes to computational biology. Association studies associate signals with phenotypes. However, it is not yet clear where in the sequence data the signals will be found. Antibodies and TCRs are three-dimensional structures whose avidity for antigen depends on multiple contact surfaces. The relationship between sequence and structure is complex. Different sequences can have convergent structures (Scheid et al. 2011), and the same sequence can encode multiple conformations (James, Roversi, and Tawfik 2003). However, simpler properties like gene segment usage, CDR3 length and charge, and mutation frequency may also provide signals. The answers to these debates may emerge from computational analysis of large datasets.

Overall, the convergence of knowledge and technologies offers the hope of being able to monitor the immune system in all its complexity. The tools and techniques that the new technologies provide offer the chance to approach the immune system at its “native resolution”—at the level of individual cells and molecules, and on its immense scale. Inevitably, this convergence will contribute to deeper understanding across the spectrum of conditions in which the immune system plays a role, as well as to a new generation of vaccines.

5.4 INFRASTRUCTURE NEEDS

Historically, the practice of medicine has been anchored in the knowledge base and traditions of taxonomic biology-based research. As a result, hypotheses are based upon phenomenological observations rather than fundamental laws. An interesting analogy can be drawn with the Japanese postal service, a system for which there is no logical connection between addresses and locations. This organically developed system is effective but also requires the postal worker to memorize the mail route. That “local knowledge” is not translatable. For instance, if the postal worker is given a new route, the whole process of learning how to deliver the mail begins again. Biology (and medicine) are similar fields of intense specialization, where specific knowledge of a particular signaling pathway, for example, takes years to acquire and does not necessarily help when learning about a different area of biology or even signaling pathway! But disparate fields are converging, and the challenges of one discipline, (e.g., biology), can be offset by the specialization and tools of another (e.g., physics and engineering).
As an example, take single-cell analytics. Using new nanotechnology-based separation and analysis tools (Fan et al. 2008), it is now possible to perform quantitative measurements, for example, measuring for a particular biomolecule in its abundance either in copy number or in a cell-by-cell basis. This is becoming true for measurements of transcripts and proteins as well. However, a single cell, as compared to a pool of cells (or related piece of tissue), is a finite system. In a thermodynamic sense, this means that each cell exhibits individualized fluctuations; thus, a quantitative measurement of a specific parameter in one cell will yield a different answer when measured in an identical cell separated in time. Statistical variations of such measurements across many single cells define the fluctuation ranges, and these maps can provide the basis for predictions of behavior of large pools of cells.

Over the next ten years, the major scientific infrastructure needed will be an effort to define these “laws of biology” within a convergence approach that nurtures engagement of the physics and physical sciences research communities. In an effort to do this, several universities and research institutions have been establishing interdepartmental institutes that draw on multidisciplinary science groups that are co-located within a single institute and work towards solutions jointly. Examples of contemporary institutes designed using this model include the Clark Center, which houses the Bio-X program at Stanford University, the Koch Institute at MIT, the Wyss Institute at Harvard University, the Petit Institute for Bioengineering and Bioscience at Georgia Tech, the Molecular Engineering Institute at the University of Chicago, and the North Campus Research Complex at the University of Michigan (Sharp and Langer 2011). The successes of these models in improving productivity and innovation in research need to be better understood and then compared with “traditional” organizational research models. These new best practices can then be adopted across many more research institutions to enable the development of robust nationwide convergence-style research infrastructure.

5.5 R&D STRATEGIES

Enabling and supporting convergence requires astute initial investment. To this end, governments should establish funding programs that support convergence of different research fields (engineering, physics, biology, medicine) in the attempt to benefit from communication and learning a “common language” and as a result building a “whole which is bigger than its contributing parts.” When possible, these funding initiatives should leverage large multidisciplinary academic centers, like those described in the last section, that demonstrate high levels of innovation, creativity, and productivity as compared to smaller efforts led by single investigators. A companion objective should be to include scientists from social science research areas—economics, anthropology, psychology, and sociology, to name a few—to provide additional insight. One option to enable this integration would be a National Converging Technologies Initiative. This effort would help coalesce convergence experts and expose research opportunities and funding needs, much as the National Nanotechnology Initiative (NNI) and the High-Performance Computing and Communications (HPCC) effort have helped coordinate and spur activity in nanotechnology and computing, respectively.

There is no substitute for predictable and sustainable funding mechanisms to support the advance of convergence in medicine. However, that funding must be coupled with a rigorous peer-review process that includes reviewer groups with a broad array of expertise to handle the unique interdisciplinary complexities of convergence-related research. Realizing convergence-style reviewer groups may necessitate novel approaches such as providing opportunities for experienced program managers and reviewers from Federal agencies to take on short-term assignments in other research agencies. For example, think-tank environments could be established within each research agency, and agency detailers from across the Executive Branch could be invited to visit for several months to collaborate on the convergence-related research priorities of the host institution. This might be coordinated by the National Science and Technology Council.
Figure 5.7 Examples of academic/government-sponsored and industry-sponsored IT research and development efforts in the creation of commercial products and industries (NRC 2012, Fig. 1, p. 3; © 2012, The National Academies Press, used by permission).
A comprehensive, long-term R&D investment strategy for convergence, as with any paradigm-shifting scientific endeavor, involves bringing together stakeholders who did not work together jointly in the past (as is often the case for fields undergoing convergence), and it will take time to show results. A high expectation of a long-term funding commitment is required. As exemplified in Figure 5.7 (previous page), considerable and consistent Federal investment forms the basis for a system of feedback loops that enables industry to engage and reengage at various points.

Convergence is a new approach to science, collaboration, and cross-cutting interaction, and thus it is a lasting proposition that would be well served with consistent funding—funding that should be allocated within the “convergence account” to the most promising areas. Such funding must be flexible enough that it can be reallocated to high-impact opportunities as they emerge.

### 5.5.1 What are the Overall Emerging Topics and Priorities for Converging Technologies Research and Education?

Integration of convergence into everyday life will require parallel engagement of society in defining acceptable objectives and setting agreed boundaries. These evolving standards will define how future technologies are developed and implemented in everyday life and how future technology developers and scientists are being trained. Let us use an example of “nanotechnology,” because the emergence of this term in public discourse provides some recent guidance. Whereas the term “nanotechnology” itself has little specific reference in popular culture, fear of the interface between human biology and physical machines is widely present in popular science fiction movies and television shows—from the *6 Million Dollar Man* and *RoboCop* to *Star Trek* and *The Terminator* (Figure 5.8). To explore the public perceptions around the topic of nanotechnology, in 2008 the Center for Nanotechnology in Society at Arizona State University and its collaborators at North Carolina State University conducted the nation’s first National Citizens’ Technology Forum on the topic of nanotechnology and human enhancement. The study focused on citizens in six sites across the United States. Each of the groups consistently expressed concerns about the effectiveness of related regulations and doubt about equitable distribution and monitoring. The groups also placed greater importance on therapeutic rather than enhancement research and requested greater public information and education, especially in K–16 education, about these technologies (Hamlett, Cobb, and Guston 2008 and Guston 2010).

![Image](https://example.com/image1)

**Figure 5.8** Public perspectives of science and technology spanning the human condition (images, Creative Commons).
It is clear that the interaction between technology (human-made) and biology (nature-made, or God-made, depending upon one’s perspective) can provoke responses that are strongly influenced by personal values. Research of Yale Law School’s Cultural Cognition Project demonstrates that, “Cultural cognition … causes people to interpret new evidence in a biased way that reinforces their predispositions. As a result, groups with opposing values often become more polarized, not less, when exposed to scientifically sound information”. Dan Kahan of Yale University (Kahan 2010) argues that: “We need to learn more about how to present information in forms that are agreeable to culturally diverse groups, and how to structure debate so that it avoids cultural polarization. If we want democratic policy-making to be backed by the best available science, we need a theory of risk communication that takes full account of the effects of culture on our decision-making.”

In addition to religious values, perspectives associated with the environment, economics, social justice, and other issues play key roles in the reactions that individuals and groups have to emerging and converging technologies. Working towards potential strategies, David Guston of ASU’s Center for Nanotechnology in Society envisions a process of anticipatory governance, or an effort to manage the social understanding and reception to emerging knowledge-based technologies while such management is still possible. This includes three critical components: foresight (of plausible future scenarios), integration (of social science and humanities research with nanoscale science and engineering), and engagement (of publics in deliberations) (Guston 2010).

Various efforts have been undertaken to avoid a negative public perception of emerging technology in reference to nanotechnology. The Nanoscale Informal Science Education Network (NISE Net) conducted a series of public forums at five sites across the United States focused on nanotechnology and health and personal care. These public engagement programs enhanced attendees’ understanding of nanotechnology, its potential impact, attendees’ awareness of benefits and risks, and their confidence in expressing and supporting their viewpoints about nanotechnology (Flagg and Knight-Williams 2008). For instance, after hearing experts speak on the topic of nanotechnology improvements, they were asked whether they agreed or disagreed with the statement “new nanotechnology applications in medicine should be made available for use before we understand the possible risks.” Participants generally disagreed with this statement when the application was sunscreens, but agreed with it when the application was cancer therapies (Kollmann and Reich 2011).

If there is an interest in addressing these concerns and in engaging and including societal understanding in emerging technologies, it could prove prescient to develop a Center for Communication and Societal Engagement for Converging Technologies. Such a center could offer expert assessment in anticipation of potential future applications and couple that information with public education efforts to encourage fact-based dialogue among the citizenry. This center could also drive opportunities for training in science communication and in the societal and ethical implications of technology into all graduate and undergraduate science curricula. This center would need to be an independent nonprofit organization working closely with funding agencies, national labs, universities, and industry to identify scientific frontiers emerging within public discourse.

Together these new elements of governance, outreach, and public engagement could develop a network capable of supporting educational enrichment in emerging frontiers among the general public and at all grade levels, especially 7–12. Widespread public engagement in policy considerations and in the related governance of converging science and technology development will be critical. Research of this sort is important in charting a course and establishing educational objectives associated with the development of converging technologies so that years of work and funding are not wasted by a mismatch between public support and research and development trajectories.

3 See Chapter 8 of this report for a greater discussion regarding how converging technologies should shape science, technology, engineering, and mathematics (STEM) education in levels 7–16.
5.5.2 What is the Impact of Converging Medical Technology on Society?

Among the most important societal implications for converging knowledge and technology in medicine will be the redesign of foundational decision-making and choice. The conventional practice of medicine today is reactive and seemingly in diametric opposition to the tenets of preventative medicine (NRC 2011). In fact, the current system is rather ineffective in fostering long-term wellness at the level of individuals or larger cohorts. This inadequacy is based on several fundamental issues. First, current systems are, by and large, based on the assumption that participants (doctors and patients) are rational actors who, when presented with adequate information, will make better decisions at an individual and group level. Unfortunately, “adequate information” about health and cost consequences of daily action and inaction is not yet truly available. Second, most current medical practitioners were trained in a “standard of care” context that is typically exemplified by reacting to illness rather than preventing onset. Third, “medicine” as an institution is risk-averse and opposed to dramatic change. In the short term, the system rewards consistency, (i.e., standard of care), while the long-term goals, especially those that present risk, liability, or potential sacrifice, are discouraged.

However, new models are emerging from research labs and also from ad hoc experiments in governance, especially those coming from virtual communities on the Web. Vast amounts of data about human behavior are making robust behavior modeling more useful. Leveraging this data and making it meaningful for decision-making will also be crucially important. Working with new insights about people—human behavior and cognitive capacities—combined with knowledge of organizing structures and processes will point to new ways of ordering society at a global level. Global modeling and modeling of complex systems will bring about another wave of decision-making tools for business and governments.

5.6 CONCLUSIONS AND PRIORITIES

As discussed throughout this chapter, convergence as a policy and a funding focus is central to driving biomedical progress. Converging technologies will impact economic competitiveness by enabling a better understanding of costly social health phenomena via better analysis and integration of big data. Convergence will also enhance human capacity with significant goals like developing cancer therapies that have no side effects. (Imagine approaching taking a chemotherapy drug like you would an aspirin.) Finally, while not discussed at length in this chapter, converging technologies have the potential to impact national security because many of the resulting advances will lead to the democratization of cheap and available tools that will enhance healthcare outcomes and save lives: As many social science studies have shown, there is a strong correlation between social justice and new medical and social technologies and between the dueling frameworks of access to healthcare and the potential for violence in a society (Farmer 2003).

Success in these areas, however, is dependent upon a clear and consistent course of action—a trajectory of research and development, public communication, education, and engagement—that enables scientists, engineers, and various stakeholders, including the public, to engage in development of the goals and strategies that will make the promise of convergence in health research a reality.

5.7 R&D IMPACT ON SOCIETY

Convergence for health, the new kind of alchemy we discuss throughout this chapter, is not only promising for the reasons discussed above but is also our society’s best option to avert challenges we face in the area of healthcare access and infrastructure.

The United States spends a larger portion of its gross domestic product (GDP) on healthcare than any other major industrialized country, and healthcare is one of the fastest-growing components of the Federal budget. Total expenditure on healthcare is now above $2.5 trillion, almost one-fifth
(17.6%) of the U.S. Gross Domestic Product (PBS News Hour 2012). These statistics continue to climb, with national health expenditures expected to increase an average of 5.7 percent per year over the projection period of 2011-2021 (CMS 2011). This burden is increasingly felt at home, with the National Center for Health Statistics reporting that as of 2009, the per capita annual healthcare expenditures topped $8,086 (NCHS 2012, 370, Table 125).

The challenge to our society becomes clearer by looking at the contrast of high expenditures and low access. For instance, between 2000 and 2010, the percentage of adults with private insurance declined from 71% in 2000 to 60% in 2010, and persons 18-44 years of age who were uninsured increased from 22% to 27% during the same period (NCHS 2012, 14, Figure 9).

In addition to high cost and poor access to care, our society also faces a huge demographic shift that will push our existing healthcare infrastructure to the brink. This is a two-fold issue. First, biomedical advances prolong American lives. Consider that Americans born at the end of the 20th century can expect to live about 30 years longer than if they had been born in 1900 (Murphy and Topel 2006), and most retirees in their 60s and 70s are physically able to work (Maestas and Zissimopoulos 2009).

Second, this longer lifespan is translating into increasing costs for enhanced end-of-life care due to aging-associated complex diseases. Just as cancer recently replaced heart disease as the leading U.S. cause of death (thanks to major advances in heart-disease treatment), some expect brain diseases to displace cancer in upcoming years. Alzheimer’s disease, for example, will affect the baby boomers at such an alarming rate that it is unclear how our current healthcare system will cope with it. According to the Alzheimer’s Foundation (2010; Hebert, Scherr et al. 2003), “the number of people aged 65 and older with Alzheimer’s disease is estimated to reach 7.7 million in 2030—more than a 50 percent increase from the 5.1 million aged 65 and older currently affected.” Unfortunately, the average annual cost of a Medicare patient with Alzheimer’s is three times that of a patient without. Medicare spent $91 billion on patients diagnosed with Alzheimer’s disease in 2005. Future projections include $189 billion in 2015 and an increase to over $1 trillion by 2050 (Swartz 2010).

The best way for science to contribute to this alarming situation is to ease the demographic shift through the development of new health technologies to address disease burden and number of individuals affected, and to enable this wave of aging citizens to remain a productive part of the workforce for a longer time. Such an effort would allow the attending healthcare costs to be spread more evenly over an extended period and across the population base.

Converging knowledge and technology for society (CKTS), and the corresponding transformation of healthcare it can trigger, is a key component to buying our society the time we will need to innovate our way through the dramatic challenges outlined above.

5.8 EXAMPLES OF ACHIEVEMENTS AND CONVERGENCE PARADIGM SHIFTS

5.8.1 Wellness-Focused Contemporary Medicine

Contact: Piotr Grodzinski, National Cancer Institute, National Institutes of Health

A convergence of several disciplines to enhance capabilities of medicine has been occurring for several years. It has led to introduction of many technologies that have enabled breakthroughs in both research capabilities and practical clinical and medical practices. Several of these examples were discussed in the Vision (5.1) and Goals sections (5.3) of this chapter. To review a few important ones:

- Discovery and implementation of magnetic resonance imaging (MRI) and positron emission tomography (PET) have dramatically improved the capabilities of imaging techniques and have led to new modalities of detecting cancer and other diseases.
• Establishment of high-throughput, inexpensive sequencing techniques allowed for successful completion of the Human Genome Project; these techniques are used now to sequence several types of cancer under a large initiative, the Cancer Genome Atlas at the National Cancer and National Human Genome Research institutes.

• Sequencing efforts, which produce large amounts of data, in turn contribute to further expansion of bioinformatics and sophisticated data analysis techniques.

Such new technological and engineering advances will continue to enrich medicine and will continue to change ways future medicine is practiced. We should expect disease diagnosis to become more accurate, with several tests performed by patients at their homes and treatments becoming more effective.

Although implementation of new technologies into medicine improves people’s lives significantly, it is not a decisive factor alone when it comes to society’s health and wellness. As described in Section 5.7, R&D Impact on Society, of this chapter, the United States spends over 17% of its GDP on medical care. This is partially due to the use of expensive and sophisticated medical technologies often used towards the end of a patient’s life. For example, the United States ranks second, after Japan, on the availability of MRI units. The average MRI instrument costs over $1 million, and tests performed with this equipment are also expensive (Conference Board of Canada 2013). Also, despite the use of sophisticated technologies; life expectancy at birth in the United States ranks as only forty-fifth among all countries in the world (UN DESA 2011), most likely due to the uneven access to healthcare (see Section 5.7).

Lifestyle, eating habits, and access to medical care play very significant roles in determining overall wellness. In order to leverage all these factors in the future, models of medical care will need to shift from reactive—treating the disease after the patient already succumbed to it—to proactive and preventative—working hard on educating society, implementing healthy lifestyles, and expanding further approaches to screening and vaccination, when appropriate. We have already made significant strides in some of these areas; for example U.S. smoking rates are significantly down from the peak of 45% of adults in the mid-1950s to about 20% of adults today. Cigarette smoking is considered the leading cause of preventable death and is responsible for over 400,000 deaths per year (CDC 2012). Wellness also is a function of mental/neural health and mental happiness determined by a summation of factors that include societal relationships. This component is growing in importance with the expansion of societal interactions and with the population aging.

Healthy lifestyles are not only related to diet and personal habits, but also to the environment in which we live, work, and rest. There is an effort to improve construction practices to achieve high-performance and sustainable buildings with optimized energy efficiency, conservation of water use, enhanced indoor environmental quality, and reduced environmental impact of used construction materials (see http://www.wbdg.org/references/fhpsb.php). The Federal Government is aggressively implementing these guidelines in the management of the approximately 450,000 buildings it owns and in the construction of new ones. A correlation between workers’ productivity and health with the design of a building with appropriate lighting, ventilation, and control of air contamination has been well documented (e.g., http://www.wbdg.org/design/promote_health.php). An implementation of novel construction methods to improve the in-house environment and conserve energy, in combination with distributed sensor technologies, will lead to the development of “smart homes” capable of sensing the local environment and then, in conjunction with knowledge of inhabitant behaviors, allowing for “smart” adjustment of indoor environmental conditions (Tonn 2013).

Future efforts to improve health and maximize human potential will need to rely not only on convergence and implementation of new technologies into medical care, but foremost on taking a holistic approach to creating wellness environments in the places where we live and work.
5.8.2 Physical Sciences and Engineering Applied to Oncology

Refer to: WTEC Assessment of Physical Science and Engineering Advances in Life Sciences and Oncology in Europe (Janmey et al. 2012)

R&D projects have begun in the United States and Europe to invite physical sciences and engineering researchers to work with cancer biologists to rethink biomedical approaches to understanding and curing cancer. These initiatives are a response to the fact that, globally, the extensive cancer biology programs, substantial funding, outstanding talent, and state-of-the-art tools applied over four decades have been unable to meaningfully reduce cancer mortality rates. In the United States, a new NIH Office of Physical Sciences-Oncology began in 2008/2009 to award cooperative agreements to U.S. universities in a collaborative network of now-12 physical science-oncology centers that unite experts in the fields of biology, medicine, physics, chemistry, mathematics, modeling, informatics, engineering, and nanotechnology to address cancer. Interdisciplinary, transnational cancer research efforts also have begun in Sweden, France, Germany, and other EU countries, all with robust funding despite global economic uncertainties. U.S. and EU physical sciences oncology programs span the following broad categories of research (Janmey et al. 2012):

- Information and complexity
- Extracellular and tissue microenvironments
- Cell and tissue mechanics
- Cell transport and metabolic waste removal processes
- Dynamics to understand and measure the rates and patterns of cell shape, change, migration, and division and their integration with biochemical and genetic information
- Application of new devices and diagnostic principles to exploit the physical properties of tissues for cancer diagnosis and treatment

The work of the NIH Physical Science–Oncology Centers (http://opso.cancer.gov/centers/) is helping to define a “soft-matter physics” or “physics of cancer,” looking in part at tissue boundaries as comparable to fluid boundaries. It is hoped that such novel applications of physical science and engineering to oncology will bring breakthrough solutions to cancer mortality due to tumor growth and metastasis.

5.8.3 List of Examples

<table>
<thead>
<tr>
<th>CKTS Domain</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer detection and treatment with reduced side effects</td>
<td>Combining nanotechnology devices with recent advances of cancer biology to develop new platforms for delivery of localized therapies and new multiplexed and sensitive diagnostics</td>
</tr>
<tr>
<td>Health data analysis and delivery for real-time health monitoring towards wellness</td>
<td>Combining advanced electronics, sensor technologies, and physiology to develop self-based or embedded wearable body function monitoring and to design ‘smart homes’ for improved interaction of living environment and the individual</td>
</tr>
<tr>
<td>Regenerative medicine and advanced prosthetics</td>
<td>Using advanced fabrication technologies to create in vitro environments for cell and tissue growth to create artificial organs. Through combination of advanced electronics, design techniques, and ability to monitor brain signal activity, creating advanced prosthetics with seamless interconnectivity of the artificial limb and the human body</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>CKTS Domain</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harnessing the human immune system to develop next-generation vaccines</td>
<td>Using advanced technologies for functional characterization of single immune cells and monitoring of vaccine responses to measure new vaccine efficacy</td>
</tr>
</tbody>
</table>

5.9 INTERNATIONAL PERSPECTIVES

The following are summaries relevant to this chapter of discussions at the international regional WTEC NBIC2 workshops held in Leuven, Belgium, September 20–21, 2012; in Seoul, Korea, October 15–16, 2012; and in Beijing, China, October 18–19, 2012. Further details of those workshops are provided in Appendix A.

5.9.1 United States–European Union NIBIC2 Workshop (Leuven, Belgium)

Panel members/discussants:

Laura Ballerini (co-chair), University of Trieste (Italy)
Miloš Nesládek (co-chair), Hasselt University (Belgium) and Minatec
Jian Cao, Northwestern University (U.S.)
James Olds, George Mason University (U.S.)
Mark Lundstrom, Purdue University (U.S.)
Mira Kalish Marcus, Tel Aviv University (Israel)
Sylvie Rousset, CNRS (France)
Christos Tomakanis, EC (EU)
Robert Urban, Massachusetts Institute of Technology (U.S.)

The working group convened via the United States–European Union NIBIC2 Workshop in Leuven, Belgium, resulted in three distinct focus areas that were proposed to represent tractable, high-impact opportunities for human health over a ten-year time frame:

1. Molecular and dynamic profiles used for personalized medical treatment
2. Quality-of-life enhancement: prosthetic devices and regenerative medicine
3. Personalized innovative education

These three opportunity areas are described in more detail below.

1. Molecular and dynamic profiles used for personalized medical treatment of cancer or neurodegenerative disease, as well as more acute conditions such as in context infection or response to trauma, represent important opportunities. Critical components to drive progress in these areas will be:
   - Data optimization in the sense of innovative and enhanced data harvesting, analysing, sharing, drug surveys, and management of personalized data from an ethical point of view
   - Improvement of technological tools for information at the molecular level (proteome, genome, bioinformatics, contactless tools, biomarkers groups for disease progression versus individuals, sensors, cellular imaging, and signalling in cell biology)
   - Tools for improving accuracy and efficacy towards predictive diagnosis
   - Cost-effective, personalized manufacturing of drugs
   - Distributed systems for delivery of personalized care

Boosting innovation in industrial systems is crucial for the European Commission: developing new knowledge, technologies, products, and applications that, bridging the divide between research and innovation needs, could turn today’s societal challenges (e.g., health, well-being, ageing) into opportunities with high potential for competitiveness, innovation, and growth is a
pivotal strategy to achieve that. So, enhancing convergence of key enabling technologies (i.e., nanotechnology, nanoelectronics, advanced materials, biotechnology, photonics, etc.) should lead towards knowledge-, capital- and skill-intensive innovation cycles, driving the development of innovative industries. The joint NSF–EC workshop held in Leuven (September 20–21, 2013) pinpointed that developing and delivering more effective translatability of converging technologies “from bench to bedside” by achieving better personalized information for enhanced medical treatment could contribute to progress towards this goal. In this light, developing translational hubs that bring together converging technologies research from laboratory into applicable clinical trials can constitute a possible pathway to deliver personalized diagnostics and treatment. These can be done through different strategy lines:

- Mastering molecular information and dynamic progression of molecular profiles for personalized medical treatment using nano-enabled, nanostructured, and nanolayered structures, devices, processes, and systems is key to reducing the very high economic cost of treatments of cancer, neurodegenerative syndromes, and injuries, accounting for many billion Euros per year.

- The challenge is to bring together imaging, diagnostics, and therapeutics to provide integrated converging technologies-based “bench to bedside” solutions, translatable from lab into applications—to conceive, design, and develop innovative nanostructures, devices, and systems for the analysis and development of molecular information and dynamic progression of molecular profiles for personalized medical treatment of various diseases such as cancer, neurodegenerative disease, Parkinson’s, and spinal lesion.

- Designing and developing, enhancing, and improving innovative nano-enabled tools for enhanced personalized data harvesting, sharing, analyzing, surveying and managing, and processing the information at the molecular level. Proteome, genome, bioinformatics, contactless tools, biomarkers groups for disease progression versus individuals, sensors, cellular imaging and signalling in cell biology should be used for developing tools with improved accuracy and efficacy for personalized predictive diagnosis and treatment by cost-effective and personalized manufacturing of drugs, supported by an affordable system for delivering of care. Ethical considerations should be included.

2. **Quality-of-life enhancement via prosthetic devices and regenerative medicine** primarily relates to engineering—“of” and “for” the human body—human bionic machine/organ interfaces as new frontiers in personalized regenerative medicine. Critical components to drive progress in these areas will be:

- Nanotechnology, nanomaterials, nanoelectronics
- Artificial organs by design
- Artificial restoration of functions (sight, ear, motor functions…)
- Development of multidirectional interfacing, e.g., therapeutic interfaces
- Improved knowledge in intracellular signal transduction codes
- Addressing cognitive enhancement
- Restoring functions to restore productivity

The joint NSF-EC workshop also highlighted that convergence of key enabling technologies that can augment translatability of research “from bench to bedside” by delivering innovative engineering systems “of” and “for” the human body, prosthetic organs “by design”, and new human–bionic machine/organ interfaces. New research concepts in cellular interactions with artificial man-designed nanomaterials are needed to provide innovative rules in the design of interfaces that can subsequently be applied to creating and integrating tissues *in vivo*, improving control of tissue development, and tuning tissue performance. These novel interfaces could also be based on nano-enabled and/or nanostructured surfaces providing innovative properties for new nano–bio functionalities. Tissue engineering aims at developing
functional substitutes for damaged tissues and organs, where the increased understanding of the mechanical and physical environments that cells need to form functional tissues has contributed to promoting research into the converging technologies domain and into the nanoscaled features ultimately instructing tissue regrowth or repair.

The core ideas are to:

- Conceive, design, and develop innovative engineering systems “of” and “for” the human body
- Provide innovative functionalities for delivering new human bionic machine/organ interfaces as new frontiers in personalized regenerative medicine
- Apply and use in a converging mode converging technologies, nanotechnology, nanomaterials, and nanoelectronics, making them work together to deliver “artificial organs by design” and new ways to provide affordable and viable artificial restoration of functions (e.g., sight, hearing, motor functions)
- Address the development of multidirectional interfacing (e.g., therapeutic interfaces)
- Design and deliver new improved knowledge in intracellular signal transduction codes and cognitive enhancement in order to recover functions to restore productivity

3. Personalized innovative education would represent a major paradigm shift in addressing formal and informal education with adaptive life-long learning systems. Although this topic is not limited to human health issues, it is certainly vital to being able to address the kinds of wide-ranging CKTS needs that are discussed in this chapter. Critical components to drive progress in these areas will be:

- Targeting aging needs for continuous education though informal education processes and support for sustainable employment
- Micro-education learning platforms based on personal needs: “I teach you the way you learn”
- Adaptability of workstations to the needs of individuals in terms of tailored content and the education system taking into account the man–machine relationship
- Haptic platforms for sensory and motor feedback for personalized improved learning
- Connecting informal with formal education through science centers on CKTS
- Reframing the formal educational system to promote convergence of disciplines by mutually enabling each other (improving disciplines’ awareness of their limits and needs)
- Moving cognition to information distribution: synergies with public media
- Developing markets for targeted and personalized education

5.9.2 United States–Korea–Japan NBIC2 Workshop (Seoul, Korea)

Panel members/discussants:

Takanori Ichiki (co-chair), University of Tokyo, (Japan)
Kyu Back Lee (co-chair), Korea University (Korea)
Robert G. Urban (co-chair), Massachusetts Institute of Technology (U.S.)
Kwon Wook Kang, Seoul National University (Korea)
Young Keun Kim, Korea University (Korea)
Ickchan Kwon, KIST Biomedical Research Institute (Korea)
Kuiwon Choi, KIST Biomedical Research Institute (Korea)

The working group convened via the United States–Korea–Japan NIBIC2 Workshop in Seoul resulted in six distinct focus areas that were proposed to represent tractable, high-impact opportunities over a ten-year time frame:

1. Nanostructured materials for cancer vaccines
2. Theragnosis for personalized medicine via imaging
3. Human enhancement
4. Using bio-inspired nanomachines integrated with fabricated devices into systems
5. Optimizing stem cell function via nanotechnology-based structures
6. Developing specialized centers for health-related convergence

These opportunity areas are discussed in more detail below.

1. **Nanostructured materials for cancer vaccines** aim to improve efficiency of vaccine loading via nanotechnology via core–shell particles. Critical components to drive progress in these areas will be:
   - Iron-oxide cores with zinc-oxide coating resulting in cytoplasm-specific loading and also providing imaging modality to trace DC migration
   - Clarifications of toxicity profiles
   - Materials “safety platforms” that could be useful to expedite materials technology development
   - Multifunctional, biocompatible nanoplatforms
   - Personalization of antigens
   - Inclusion of toxicology and databases/predicative simulations
   - Leads to parenteral formulations

2. **Theragnosis for personalized medicine via imaging** will be needed to underwrite the use of expanding use of genetics diagnostics in clinical management. Critical components to drive progress in these areas will be:
   - Drug design that is based upon molecular imaging, not genotype, e.g., 90% of drugs only benefit 40% of patients
   - Investigation into why Her2 25% is expressed by only breast cancer patients, but only 50% of them benefit from Her2 specific therapy.
   - Enzyme-based diagnostics using imaging (e.g., caspase-based imaging) or folate receptor-based probes
   - Phenotype imaging and drug delivery that overlap
   - Change in regulatory requirements to facilitate a new development paradigm at the level of the individual
   - Individualized treatment, not just personalized
   - Imaging technologies within reasonable cost
   - “Safely done” imaging

3. **Human enhancement** using convergence to provide improved productivity and enjoyment. Enhancing human function is not new: glasses, teeth, and hearing aids have been available for decades, even centuries, but moving into new converging-technology-based advances, some example concepts driving progress will be:
   - “Human 3.0”: healthy, fun, convenient
   - Enhancement of normal human power (recalling the “6-million-dollar man”)


o Blood substitutes via nanoparticle-based oxygen carriers, for example, can enable new capabilities such as improving human functioning in underwater activities
o Early need to address societal concerns

4. Using bio-inspired nanomachines integrated with fabricated devices into systems integrated for detection, diagnosis, and treatment, including addressing the unsustainable cost burden of our aging society. Critical components to drive progress in these areas will be:
  o Noninvasive measurement of cell function via bioelectromechanical systems (bioMEMS)
  o Investigation of mega-collaborative cluster interactions within rich diversity
  o Capability to track intra-vital recordings via transparent windows and interfaces

5. Optimizing stem cell function via nanotechnology-based structures to facilitate stem cell use in regenerative medicine and cell therapy. Critical components to drive progress in these areas will be:
  o Building nanoscience-based structures to drive the desired stem cell maturation and differentiation in cell culture
  o Removing the need for exogenous factors such as cytokines
  o Use of nanoscience-based structures to optimize stem cells and to drive in vivo differentiation and paracrine effects
  o Treatment synergies with RNAi, micro-RNA, hormones, and physical/biological/chemical signals
  o Possible political benefits: may ease ethical constraints of using adult stem cells or induced pluripotent stem cells (iPS)

6. Developing specialized centers for health-related convergence and organizing “national need”-oriented centers to address the rapid demographic shift towards older populations. Critical components to drive progress in these areas will be:
  o Global networks focusing on research diversity and clinical need
  o High-level recruitment of experts
  o Integration of medical and engineering students and trainees
  o Exchange programs—brain exchange
  o Partnerships with medical professionals brought in to work with scientists and engineers
  o Space-sharing/collaborative teams
  o Redesign of incentives at institutions to be successful
  o Protocols for collaboration
  o International interactions, e.g., between institutes
  o “Shared-interest” person-to-person directories
  o Industrial guidance with targeted research funding support

5.9.3 United States–China–Australia–India NBIC2 Workshop (Beijing, China)

Panel members/discussants:

Xiaomin Luo (co-chair), BGI Healthcare (China)
Gordon Wallace (co-chair), University of Wollongong (Australia)
Robert G. Urban (co-chair), Massachusetts Institute of Technology (U.S.)
Ming Liu, Institute of Microelectronics, Chinese Academy of Sciences (China)
Wei Li (China)
Xiaomin Wang (China)
The working group convened via the United States–China–Australia NIBIC2 Workshop in Beijing, resulted in four distinct focus areas that were proposed to represent tractable, high-impact opportunities over a ten-year time frame:

1. “From conception through childhood” medical supportive technologies
2. Improve nanotechnology-based formulations for clinical use
3. Enable translational medicine in the context of global collaboration
4. Address chronic neurodegenerative disease

These opportunity areas are discussed in more detail below.

1. *From “conception through childhood” medical supportive technologies* focused on reducing pregnancy-related health issues, supporting birth, childhood, and motherhood via converging technology. Critical components to drive progress in these areas will be:
   - Improving *in vitro* fertilization (IVF)
   - Full term pregnancy monitoring
   - Early infancy and pre-term birth support
   - Facilitating the mother-child relationship via technology
   - Enhancing telecommuting options and flexibility
   - Preeclampsia as an example:
     - Finger postprandial glucose (PPG) waveform morphology is predictive
     - Fetal age effects PPG
     - Effects of gestational age and maternal age are predictive
     - Soluble endoglin at week 13 is a sensitive biomarker
     - All cell-free DNA in maternal DNA is also a sensitive biomarker
   - Convergence of nanosensors can be an effective new tool to improve reliability
   - New tools are also useful in measuring blood volume change related to stressful conditions

2. *Improve nanotechnology-based formulations for clinical use*, and use known physiological *in vivo* behaviors to inform specific nanomaterial design. Critical components to drive progress in these areas will be:
   - Working towards a set of known and shared standards
   - Establish fundamental correlations (between materials and biological needs)
   - Requires global data sharing and standardization and physical standard samples
   - Requires protocols for collaboration
   - Other components of the challenge:
     - High flow rate
     - Dilution is huge
     - Control degradation
     - EPR
     - Anaerobic and low pH
     - Critical micelle concentration

3. *Enable translational medicine in the context of global collaboration*: taking full advantage of large population-based science. Critical components to drive progress in these areas will be:
   - National biobanks (blood and other tissues)
   - Biomarkers-focused research efforts
5. Implications: Human Health and Physical Potential

- Large cohort studies
- Biggest of big data challenges
- Reduction to treatment in individual patient across full network
- Disease agnostic but driven by centers of excellence
- Will require NBIC-like driven leadership to facilitate (Genome Project, Particle Physics, Space in 2000)

4. Address chronic neurodegenerative diseases with Central Nervous System (CNS) embedded devices to monitor onset, deliver treatment, track efficacy, and eventually prevent disease altogether. Critical components to drive progress in these areas will be:
  - Electronic devices and related software algorithms
  - Long-term device biocompatibility
  - Defining the optimal treatment combination
  - Developing new surgical procedures
  - Integration with physical therapies
  - Measurements of progress: (1) healthcare cost per patient, (2) availability, (3) vitality
  - Engagement with society and ethical teams early in development.

5.10 REFERENCES


Goetz T. 2008. Cancer and the new science of early detection, Wired p. 82


Tonn, B. 2013. Personal communications.


