CHAPTER 1

INTRODUCTION

1.1. NANOMEDICINE: A GLOBAL VISION

This monograph describes emerging interdisciplinary frontiers created by the fusion of nanotechnology, engineering, and medicine that provide a global vision to produce breakthrough approaches for meeting our current and future healthcare challenges. Traditionally, nanomedicine is defined as the application of nanotechnology to medicine; nanobioengineering is often used to describe nanotechnology applied to bioengineering, which includes imaging, sensing, diagnostics, blood fluids, and tissue engineering. This book brings a much-needed integration of nanomedicine and nanobioengineering to produce a broadened nanomedicine platform that utilizes nanotechnology to generate exciting new approaches for diagnostics, bioengineering, and targeted therapy. Such an integration could lead to multifunctional nanomedicines that can, as a single formulation, be used to diagnose, treat, and evaluate treatment effectiveness in real time. Collectively, these agents are termed nanotheranostics.

We live in a complex world where our health is determined by an interplay of our genetic inheritance, the environment we live in, and the lifestyle we choose. As the barriers between social, ethnic, religious, regional, and national divides come down and the world becomes a melting pot for the human race, healthcare issues (whether genetic, environmental, or lifestyle originated) do not remain localized. Today these issues are not the problems of a specific

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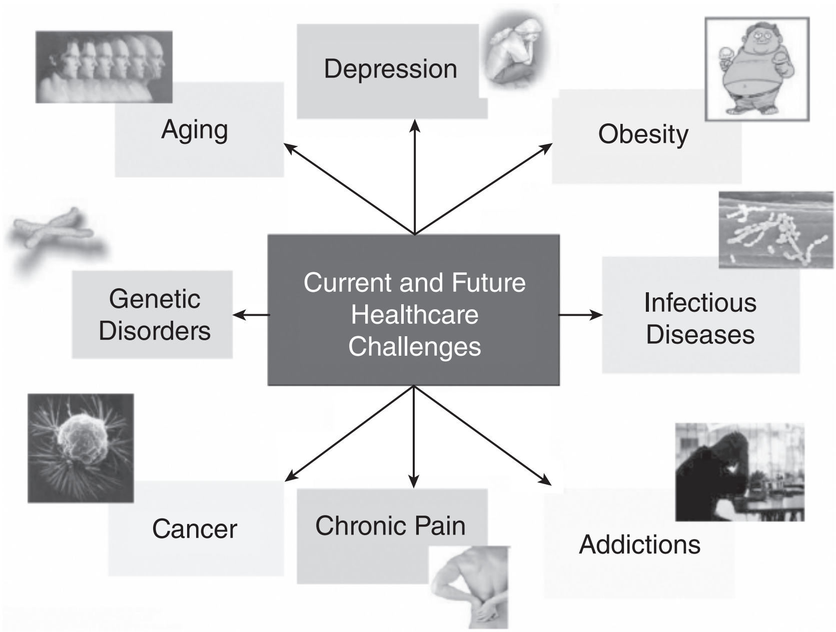

Figure 1.1. Current and future healthcare challenges.

society or a specific nation, but a global concern and global priority. As technological advances facilitate rapid travel through geographic variation, different time zones, and diverse climates, infections are no longer confined to their old boundaries and instead travel all over the globe, spreading like wildfire. Thus, as new healthcare challenges emerge in the future, we must face them together as a single global community and find effective solutions for them collectively.

The healthcare challenges that we now face and can anticipate for the future are many, and they pose an almost insurmountable task for us. Figure 1.1 lists some major challenges that our global community faces. Despite tremendous progress in winning some cancer battles, cancer remains a major healthcare challenge. Take, for example, pancreatic cancer, the survival rate for which beyond five years after detection using the current diagnostics is only 4%. Consequently, there is a need for early diagnosis, preferably at a precancerous stage when many options to treat may be available, as well as for a more effective treatment. Some treatments for cancer can be very harsh, where the patient's quality of life is seriously compromised. A more effective treatment or an alternative gentler therapy would be of significant value to such patients. New strains of infectious diseases, as well as existing ones, are another major challenge we face. New infections such as the bird flu or swine flu may originate in one small region, but it does not take long for them to spread around the world and become a pandemic. Infections such as tuberculosis and malaria, often referred to as poverty-related diseases (PRDs), are on the rise and spreading worldwide. Diseases that are manifestations of genetic disorder are again on the rise worldwide, as a result of a complex interplay of our genes, the environment, and our dietary intake. Depression and chronic pain are other healthcare problems what are highly detrimental to the quality of life that we wish to have.

Then there are healthcare issues that we create by the lifestyle we choose. The examples given in Figure 1.1 are obesity and addiction. Obesity rates are rapidly rising, and of particular concern is child obesity. Obesity creates not only physical handicap, but also a cascade of other disease manifestations, such as diabetes and cardiovascular diseases. While obesity may start in many cases from a lifestyle of eating unhealthy and fattening food, it soon becomes a biochemical addiction in which overactive bad genes in the brain create a constant need to eat. Similarly, addictions to medication, drugs, and alcohol are biochemical in nature, generating specific biochemical signatures in the brain—again, produced by the lifestyle we choose. Such addictions have now become major health issues worldwide.

Aging is not a disease, but it does affect quality of life and increases an individual's vulnerability to various diseases and infections. The world's population is aging. Accordingly, more people are suffering from neurological disorders such as Alzheimer's disease, impairment of body functions, chronic pain in joints, loss of hearing, and a reduction in eyesight. While we cannot permanently reverse aging (for which we must wait for rejuvenation therapy, discussed in Chapter 16, to develop), we can certainly use new medical advances in utilizing stem cells (discussed in Chapter 17) to replenish nonfunctioning cells, and tissue engineering (presented in Chapter 18) to replace nonfunctioning organs. We can also explore the promise of gene therapy (covered in Chapter 14) and stem cell therapy to treat neurological diseases, as well as to effectively boost the immunity to fight infections (discussed in Chapter 15). This book will address how an integrated nanomedicine platform provides new, revolutionary approaches to tackle these major healthcare issues.

1.2. THE NANOTECHNOLOGY REVOLUTION: REALIZATION OF ASIMOV'S FICTION

Nanotechnology is an emerging discipline of science and technology that has captured the imaginations of the world. Many countries have recognized nanotechnology as a national priority and allocated major resources to develop this area. It has a high societal impact, because it provides promising new solutions to numerous technical needs that the world faces (subject of global priorities), some of which are listed in Figure 1.2. In commonly adopted definitions, nanotechnology deals with materials, structures, and devices that are of dimensions in the range of 1–100 nanometers (1 nanometer is one billionth of a meter;

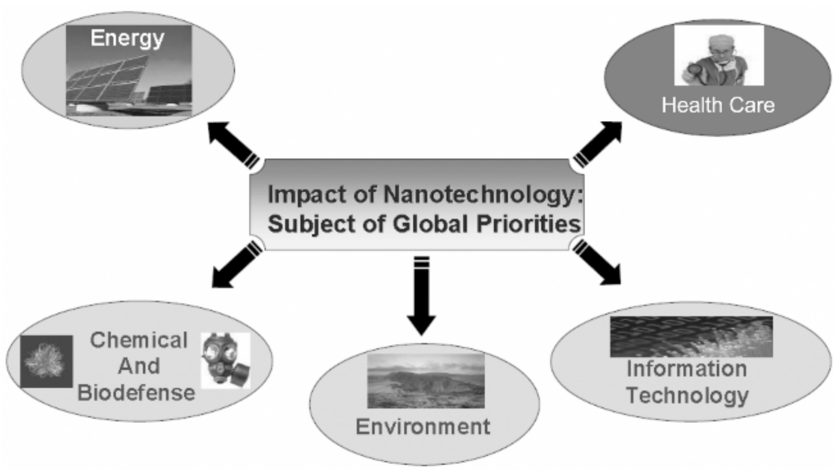

Figure 1.2. Examples of global priorities on which nanotechnology has made an impact.

nanometer abbreviated as nm) and thus are so ultrasmall that they cannot even be seen under a normal optical microscope. In reality, nanotechnology is not so new. Although it is hard to place an exact period when it was introduced, there are plenty of examples of their use in the production of tinted glass widely used in cathedrals and churches from the medieval period onwards. A beautiful example is shown in Figure 1.3, which is from the cathedral of Notre Dame in Paris. It was not until 1860 that Michael Faraday actually recognized that these bright colors in the glass were imparted by metallic gold or silver nanoparticle inclusions formed during glass processing. However, many consider Feynman as the father of modern nanotechnology when he stated in his famous lecture of 1970, "There is plenty of room at the bottom. . . ." This referred to the fact that many, many objects (particles or structures) of nanometer dimensions can be packed even in a small volume.

A major impact area for nanotechnology is healthcare. A nanoscale object (such as a nanoparticle) can provide new approaches to diagnostics and therapy, which constitutes the field of nanomedicine. Such developments demonstrate a realization of the fiction novel *Fantastic Voyage* by Isaac Asimov in 1966, which was later dramatized in a film by Richard Fleischer. These works presented a visionary fiction in which a submarine carrying a crew and a medical team was reduced to microscopic size and injected into the bloodstream of a diplomat. As depicted in Figure 1.4, the submarine navigated to a blood clot, which was then zapped with a laser beam to remove it and thus save the diplomat. In 2002, we used the term "nanoclinics" to describe the modern approach of using nanoparticles as carriers for targeting and circulating agents that can be directed to a desired biological site in a body. These nanoparticles can be armed with various diagnostic probes to provide on-site diagnosis and then treat and/or repair a disease manifestation. (For a more

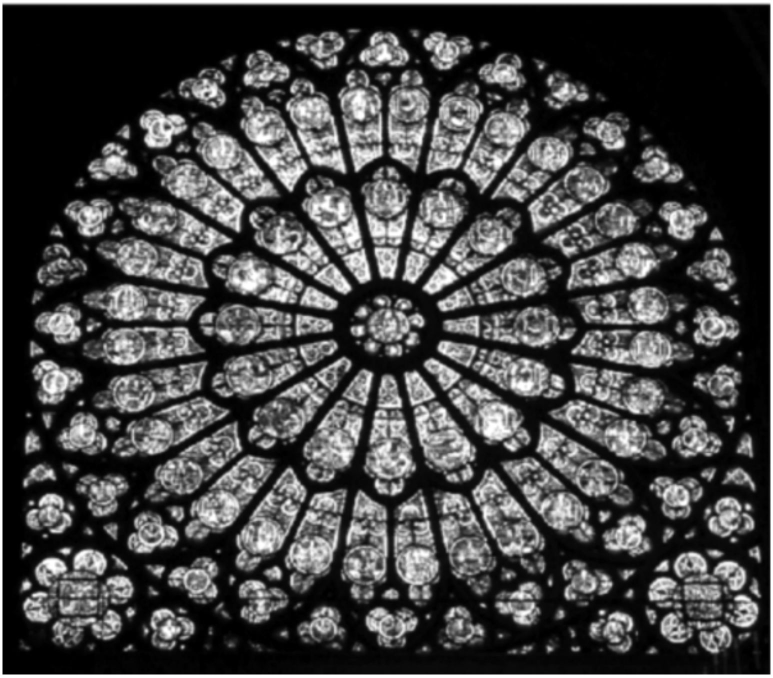

Figure 1.3. Metallic nanoparticles doped stained glass windows in Notre Dame Cathedral in Paris.

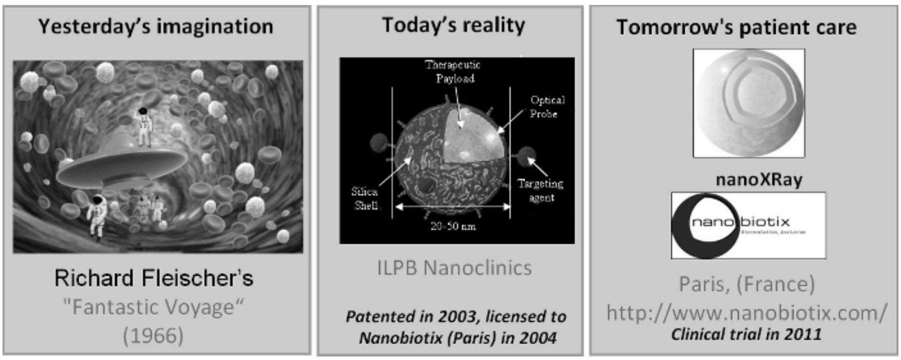

Figure 1.4. The imaginary nanosubmarine in the 1966 science fiction movie *Fantastic Voyage*, shown with the concept of a nanoclinic developed by us in 2002. This technology is currently being used in a clinical trial at Nanobiotix for X-ray nanotherapy.

detailed discussion, please see Chapter 3.) This approach is an excellent example of how the imagination of yesterday can become a reality today, and it can be further refined to produce high societal impact in the future. As shown in Figure 1.4, our nanoclinic concept licensed by the company Nanobiotix has just entered a clinical trial for X-ray nanotherapy.

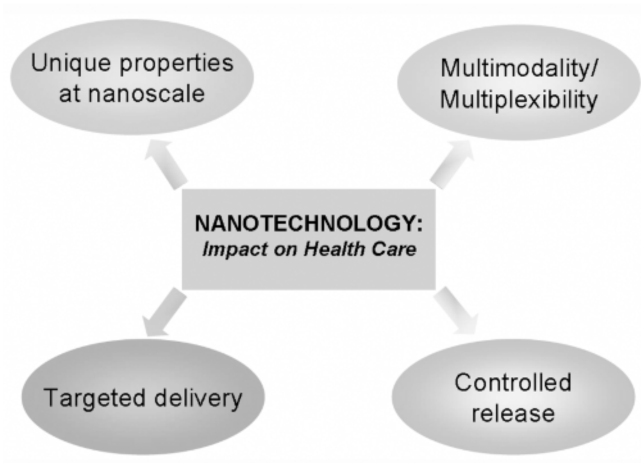

Figure 1.5. Features provided by nanotechnology that impact healthcare.

The possible impacts of nanotechnology on healthcare and society are tremendous. Some of the features offered by nanotechnology for healthcare are illustrated in Figure 1.5. First, materials, when reduced to nanometer size, exhibit physical properties that can be different from their bulk form. Furthermore, this property may become size-dependent on nanoscale. An example discussed in detail in Chapter 5 is the light absorption and emission by nanoparticles of inorganic semiconductors, such as CdSe or Si. Once their size becomes smaller than a certain length, the wavelength of light they absorb and the resulting emission color (the emission wavelength) become size-dependent. These semiconductor nanomaterials are quantum dots and quantum rods, which are presented in Chapter 5. This size dependence can be utilized for multiplexed optical bioimaging using quantum dots or quantum rods of various sizes. Another example is metallic nanoparticles, which on nanoscale are not reflective. As shown in Figure 1.3, the metallic nanoparticles exhibit bright colors derived from new optical absorptions called surface plasmon resonance bands (also discussed in Chapter 5) that do not exist in the bulk metal form. The other feature is building multifunctionality onto a nanostructure/nanoparticle platform. For example, a nanoparticle can be loaded with a number of imaging agents for multimodal medical imaging such as optical bioimaging, magnetic resonance imaging (MRI), and positron emission tomography (PET) which are covered in Chapter 8. Even in optical imaging, one can use different dyes or quantum dots combinations, and thus multiple color staining (labeling) for multiplexed optical imaging can be realized to enhance detection specificity. The nanostructured materials are promising scaffolds for tissue regeneration, an evolving field also known as tissue engineering (Chapter 18). For therapy, one can introduce a combination of therapeutic modalities such as light-induced therapy, magnetic therapy, thermal therapy, radiotherapy, and chemotherapy into a simple nanoparticle. Nanotechnology also holds promise for stem cell biotechnology, which is discussed in Chapter 17 ("Stem Cell Biotechnology").

Targeted delivery is another important feature whereby one can introduce biorecognition (by antibody or other biospecific units) on a nanoparticle to identify a specific biomarker (signature) of a disease and thus target the disease site. One can build multiple targeting ability on the nanoparticle to enhance its specificity and thus increase its targeting ability.

Controlled release of a drug or therapeutic payload carried by a nanostructure or nanoparticle is another important feature offered by the nanotechnology approach. A nanoparticle offers tremendous structural flexibility for inclusion of various payloads and their controlled release. First, the volume of the nanoparticle can itself serve as a diagnostic or therapeutic agent (pure nanoformulation). Second, a diagnostic or therapeutic agent can be attached on the surface or included in the interior of a nanoparticle. The release can be controlled in a number of ways. First, one can introduce external control by using a magnetic, optical, or radio-frequency (rf) field to break a nanoparticle or cleave a labile chemical linkage in order to release the payload. Second, one can manipulate the pores on the nanoparticle, either by enzymatic activities or by local heating using light or magnetic field, to control the release kinetics. Finally, one can take advantage of the enzymatic activities in the targeted cells to break down the nanoparticle to make the payload active.

While nanotechnology can offer many benefits to healthcare, there is also a growing concern about potential health hazards that may be caused by nanoparticles. The short- and the long-term toxicity of nanoparticles in the body must be thoroughly investigated. With the growing euphoria about the vast potential of nanotechnology in so many industrial sectors, there is also a concern that airborne nanoparticles in a workplace can lead to organ damage and health problems. Thus, nanotoxicity (discussed in Chapter 21) is an integral factor in developing nanomedicine. Therefore, for each nanomedicine application we must weigh the benefits versus the risks.

1.3. NANOMEDICINE: A NEW ERA IN PERSONALIZED MEDICINE

Nanomedicine, inclusive of nanobioengineering in its broad scope, is a nanobiotechnology utilizing a specifically engineered nanoplatform to carry various payloads for new, minimally invasive diagnosis, targeted delivery of therapeutics, enhanced efficacy of an existing therapy/treatment, and real-time monitoring of a treatment.

The scope and applications of nanomedicine, together with nanobioengineering, are highlighted in Figure 1.6. First, *in vitro* diagnosis in a laboratory to profile a disease can utilize various body fluids/excretions such as blood,

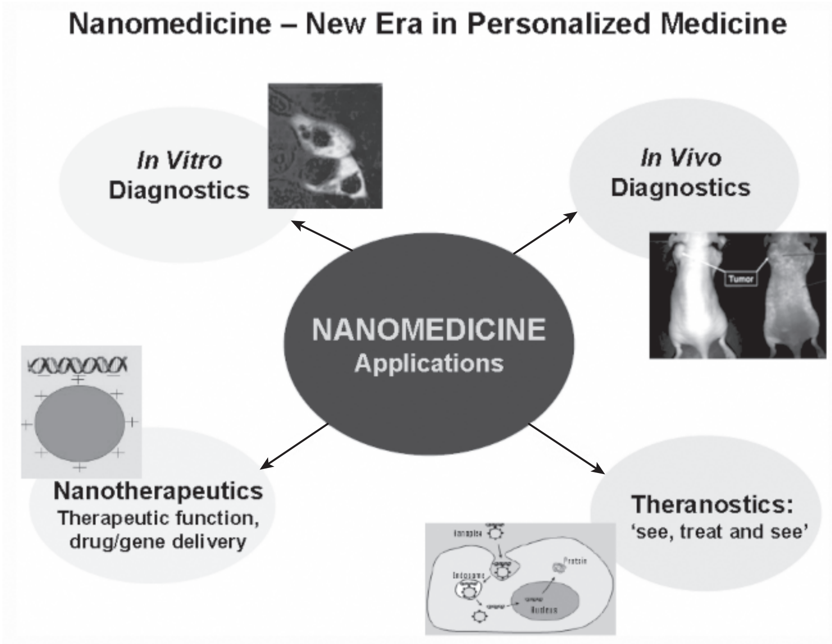

Figure 1.6. The broad scope of applications for nanomedicine.

urine, saliva, sputum, and feces. Some studies even focus on using the exhaled breath for analysis of diseases. These body fluids can interact with specially designed nanoparticles to create biological responses for identifying diseases, even at the molecular and cellular levels. This can lead ultimately to a molecular understanding of disease mechanism and sensitivity of detection at single cell levels, which can be key to early detection and personalized molecular medicine. The *in vitro* diagnosis, using a multipronged detection and quantification enabled by a nanoparticle platform, will be able to elucidate drug intake, its biodistribution, its cellular pathway, and subsequent intracellular interactions. This information can be tremendously effective in drug development and screening of various possible therapies for a given disease. Since the testing is *in vitro*, nanotoxicity is not of concern in such a scenario. For this reason, I envision that a full implementation of nanoparticle-based *in vitro* diagnosis is the first realized application of nanomedicine.

In vivo diagnosis with a nanomedicine approach offers the benefit of combining the various diagnostic modalities in a single nanoplatform (e.g., nanoparticles). For example, one can combine optical imaging and spectrometry with MRI and PET imaging to do a more thorough disease profiling based on molecular, structural, and morphological changes as a result of disease manifestations. Also, packaging them in the small nanovolume of a biocompatible nanoparticle with the ability to localize (due to the presence of targeting group) at the disease site enhances the sensitivity of detection and minimizes the potential for systemic toxicity of the imaging agent. The simultaneous presence of various diagnostic agents in the same nanoformulation also allows a medical facility to use them at the same time, without requiring separate preparation for each modality.

Of course, a major function of nanomedicine is to provide a nanoformulation that opens new modality of therapy or increases the effectiveness of an existing therapy, as well as to create the prospect of using more than one therapeutic approach in tandem. Examples of new approaches include (a) magnetic therapy using magnetic nanoparticles and (b) photothermal therapy using metallic nanoparticles. An example of improving the efficacy of an existing therapy can be demonstrated by (a) enhancing the biodistribution and circulation of a hydrophobic drug by using a nanoparticle carrier with hydrophilic surface and (b) targeting the carrier to localize a large concentration of the drug at the diseased site. Additional merits offered by nanotherapeutics include controlled and sustained release of a drug. One can control the release by manipulation of pores in the nanoparticle or external stimulation using light, magnetic field, heat, or radio-frequency field.

Finally, the biggest payoff of nanomedicine lies in the realization of theranostics, the combined function of therapy and diagnostics. In other words, the functions of targeting, effective biodistribution, multiple diagnostics, and multimodal therapy can be combined in a single nanoformulation. This allows one to follow the process of therapy to see (and monitor) a therapeutic process at work and to assess its effectiveness in real time. Real-time monitoring of therapeutic action will be of tremendous value to a patient, because one does not have to wait post treatment to determine the outcome.

1.4. NANOMEDICINE: A PROMISE OR REALITY?

In any emerging field showing great promise (and often generating considerable hype), expectations generally run ahead of the real progress. Naturally, the question may arise whether the field of nanomedicine is only a promise for the future (which may or may not materialize) or if there is evidence that nanomedicine is already impacting healthcare. This section provides a very brief account of what has been already achieved in nanomedicine.

Within the realm of *in vitro* diagnostics, in which tests are conducted in the laboratory on biological fluids outside of the body, nanotechnology is well poised to make a significant, immediate impact. There are already examples of nanoparticle-based colorimetric detection modalities, such as those used for home pregnancy kits, in which color changes are introduced by aggregation of metallic nanoparticles caused by the biomarker signature (expressions) of pregnancy. The surface plasmon resonance (SPR) biosensors discussed in Chapter 9 are widely used in biological laboratories and biomedical research worldwide.

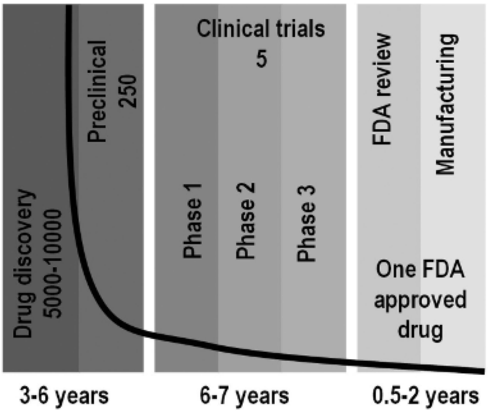

Figure 1.7. The different steps of drug development and clearance by the FDA. Data from http://www.phrma.org/.

In vivo diagnostics, nanocarrier drug delivery, tissue regeneration, and organ replacement require introduction of a foreign nanostructure in the body. The procedure for regulatory clearance [such as by the Food and Drug Administration (FDA) in the United States] is quite complex, as illustrated by Figure 1.7, and requires several steps of clinical trials.

However, several nanoformulations of drugs—such as for cancer therapy—are already FDA approved and are being used. In addition, many nanoformulations are undergoing different stages of clinical trial. Chapter 13 provides examples of nanoformulations of chemotherapy drugs for cancer treatment. Two examples are Doxil® (a nanoparticle formulation of the drug Doxorubicin, FDA approved in 1995) and Abraxane® (a nanoparticle formulation of the drug Paelitaxel, FDA approved in 2005). These are discussed in Chapter 13, along with other nanoformulations that have been approved or are in clinical trials for cancer therapy.

1.5. A NEW FRONTIER: MULTIDISCIPLINARY CHALLENGES AND OPPORTUNITIES

Nanomedicine, in its broad scope (of which nanobioengineering is a major component), is a new frontier that faces multidisciplinary challenges—from a proper formulation of nanoplatform, to bedside implementation of nanotheranostics. It thus requires a close collaboration between biologists, chemists, physicists, engineers, pharmacologists, and clinicians. Some key multidisciplinary challenges (which in turn provide opportunities for a given discipline)

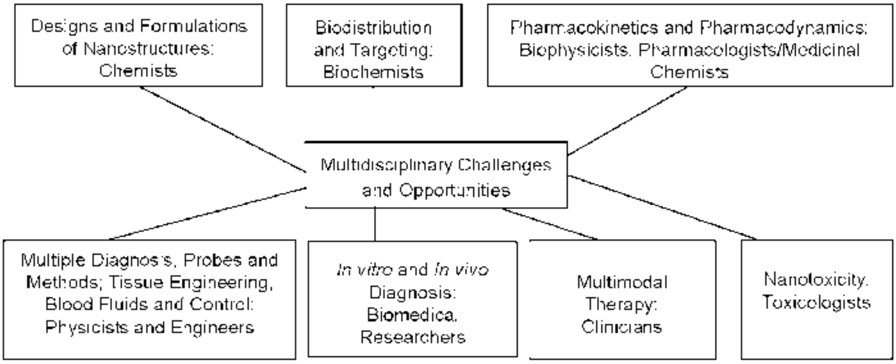

Figure 1.8. Multidisciplinary challenges and opportunities offered by integrating nanomedicine and nanobioengineering.

are summarized in Figure 1.8. For chemists, the challenges and opportunities include producing effective nanoformulations that are chemically and environmentally stable, as well as biocompatible, and that provide appropriate linkage and caging sites to attach and/or encapsulate the following: (a) various diagnostic probes, (b) therapeutic agents, and (c) groups enhancing circulation and producing targeting. Because a nanoparticle has a large surface-to-volume ratio, control of the surface composition and structure (surface chemistry) plays an important role in chemical design and synthesis. Identification of biomarkers and the selection of targeting group is another important aspect of creating a nanosize magic bullet that makes a precise hit of the target (in our case, a diseased site or a tumor). Ensuring effective kinetics of biodistribution, circulation, and selective localization of the nanoparticles at the targeted site is another important challenge that requires a multidisciplinary input from biophysicists, pharmacologists, and medicinal chemists. Multiple diagnoses, using a combination of various probes and methods and utilizing a number of physical and chemical principles, require input from physicists and engineers. A growing discipline worldwide is biomedical engineering, which cross-fertilizes biomedical sciences with engineering. This is a very welcome new discipline, which can play a major role in nanomedicine through the inclusion of nanobioengineering.

In vitro and *in vivo* diagnostics provide a comprehensive approach for early disease diagnosis, as well as for monitoring its progression and drug-induced depression. Active engagement of practicing physicians in clinical trials and subsequent translation to bedside of a patient is of vital importance. We have to engage clinicians from an early stage of nanomedicine, because their feedback is crucial in advancing the frontier of nanomedicine toward real patient care. Finally, a multidisciplinary effort is necessary to evaluate and validate the safety of nanomedicine. Toxicity concerns include chemical toxicity, immunotoxicity, organ injury, and interference in physiological functions. Hence, the continued development of nanomedicine requires thorough study at the cellular, tissue, animal, and human levels.

1.6. SCOPE OF THE BOOK: MULTIDISCIPLINARY EDUCATION, TRAINING, AND RESEARCH

Like any new frontier, advances in nanomedicine will require engagement of various disciplines as described in Section 1.5. One major challenge is that these disciplines do not even use the same set of vocabularies and acronyms. An effective cross-fertilization among these disciplines will require giving them common vocabulary terms, and the introduction of multidisciplinary concepts that can provide collaborators with the ability to understand and communicate with each other on real issues. Although a good number of books and reviews cover selective aspects of nanomedicine and nanobioengineering [e.g.: Jain, 2008; Tibbols, 2011], there is a need for a comprehensive monograph that introduces the integration of unified introductory concepts and provides a broad multidisciplinary exposure of the field to new researchers. This book is intended to fill this void and act as an introduction, providing basic concepts for the benefit of readers from the disciplines of chemistry, physics, biology, biomedical sciences, biomedical engineering, medical school, pharmacy school, and dental school, as well as from the pharmaceutical and cosmetic industries. To serve this purpose, Chapters 2–7 are designed to present basic materials, elucidate concepts, and provide an overview of the current status in meeting specific challenges of the areas covered in these chapters.

For a researcher either entering the field or interested in expanding his/her research scope, for a drug developer in a pharmaceutical industry, for a biomedical engineer interested in developing appropriate engineering tools, for a dentist applying nanotechnology for dental care, for a cosmetic industry person developing nanocosmetics, or for a clinician interested in nanomedicine therapeutic approaches, the subsequent chapters introduce specific applications and needs.

Each chapter begins with a brief outline of what the reader can expect from it, and then it ends with a highlight of the chapter. These highlights succinctly summarize the key points from the chapter, which is a very convenient listing of the take-home message from that chapter. For assisting in the teaching of this subject, each chapter also provides exercises. The chapters are written largely in a self-contained manner, so that it is not necessary to read the chapters in the sequential order as presented here—the reader can skip a chapter to move on to another one, depending on interest and need.

It is my hope that this monograph—with its comprehensive, yet introductory, coverage of the basics, applications, and needs of nanomedicine—will serve as a resource for educating and training a new generation of multidisciplinary researchers while helping to advance this new frontier toward applications needed for real patient care.

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