1 The Need for New Perspectives in Medicine

Nanomedicine is the intersection of the field of nanotechnology with the field of medicine. In order to understand the basis for this intersection, it is first important to learn a little bit about nanotechnology in general as well as a few fundamentals of medicine and specific fields of science and engineering. In this book, I will use an approach to teaching championed by Dr. Albert Baez, a Harvard professor (and father to singer Joan Baez), called the "spiral approach" to teaching (Baez, 1967). The idea is to first introduce a concept at a very simple level and then gradually peel away the layers to go into greater depth and level of understanding, like peeling back the layers of an onion. I will introduce basic concepts in earlier chapters and then go into much more detail in later chapters.

1.1 Nanotechnology: Why Is Something So Small So Big?

Nanomedicine was first popularized as a future form of medicine by futurist Robert Freitas in his pioneering initial book (Freitas, 1999), which continued in a multi-volume format. He has continued to write, not only more books on different aspects of the subject but, also, articles in scientific journals (Freitas, 2005). The idea of nanomedicine was popularized by Freitas over 20 years ago. His work helped inspire this author. While his artwork seems more in the realm of science fiction than reality, the actual writing raises many of the promises of nanomedicine and is well worth reading (Freitas, 1999, 2005). Although depicted more from the viewpoint of nanorobotics, with engineering nanomanufactured devices rather than biomimetic self-assembled nanodelivery systems, as emphasized by this author in an earlier work (Leary, 2010), his work has enthused and inspired many, including this author.

The size of the scalpel determines the precision of the surgery. Nanotechnology affords us the chance to construct nanotools that are on the size scale of molecules, allowing us to treat each cell of the human body as a patient. Human disease, while frequently described in terms of either a collection of symptoms or the organ affected, is ultimately a disease of individual cells. To understand the underlying mechanisms of human disease, it is necessary to study the disease changes at the level of the single cell. Nanomedicine ultimately will allow for eradication or amelioration of human disease at the single-cell level using large numbers of self-assembling nanomedical devices that effectively parallel-process disease at the level of millions of cells...
simultaneously. Like nanotechnology itself, which is an atom-by-atom approach to the construction of nanodevices, nanomedicine is a cell-by-cell approach to human disease. Recently a new gene-editing technology, CRISPR (Doudna and Sternberg, 2018), has allowed us to use nanomedical delivery techniques not only to perform “nanosurgery” on a single cell but even to edit a single DNA base pair (or more bases) that causes genetic diseases. In these cases, first applied to human patients in 2020, we can now practice nanosurgery on defective molecules within a single cell. We will see more and more of this in the future as well as clever uses of nanodelivery systems to target CRISPR technology to specific single cells within the human body. This will be discussed more in Chapter 9.

Since these nanotools are self-assembling, nanomedicine has the potential to perform parallel-processing single-cell medicine on a massive scale. These nanotools can be made of biocompatible and biodegradable nanomaterials. They can be “smart” by using sophisticated targeting strategies that can perform error checking to prevent harm even if a very small fraction of them is mistargeted. Built-in molecular biosensors can provide controlled drug delivery with feedback control for individual cell dosing.

If designed to repair existing cells, rather than to just destroy diseased cells, these nanomedical devices can perform in situ regenerative medicine, reprogramming cells along less dangerous cell pathways, allowing tissues and organs to not be destroyed by the treatments, and providing an attractive alternative to allogeneic organ transplants.

Nanomedical tools, while tiny in size, can have a huge impact on medicine and healthcare. Earlier and more sensitive diagnosis will lead to presymptomatic diagnosis and treatment of disease, before permanent damage to tissues and organs. This should result in the delivery of better medicine at lower costs with better outcomes.

1.1.1 Definitions of Nanotechnology Based on Size

Attempts to simply define nanotechnology in terms of a particular size range are well intentioned but overly simplistic. The National Nanotechnology Initiative included not only nanomedicine applications of nanotechnology but also its more general impact (Sargent, 2010). That size limit is often set at about 100 nm, but that is not a highly agreed-upon value. How does a nanostructure differ from conventional large proteins or other chemical molecules or polymers of a similar size?

Size alone does not make this distinction. Nanostructures are fundamentally different forms of matter than simple chemicals. Their size and organization frequently take advantage of the quantum mechanical properties of these structures to have unique properties. A simple example is the extraordinary fluorescence properties and photostability of quantum dots or nanocrystals that cannot be explained in terms of the elemental composition alone.

1.1.2 Bottom-Up Rather Than Top-Down Approach

Nanotechnology is not just based on its nanoscale dimensions. For most of human history, manufacturing came from sculpting bigger objects down into smaller objects.
1.1 Nanotechnology: Why Is Something So Small So Big?

Nanotechnology represents a bottom-up, atom-by-atom assembly (Leary, 2010) (Figure 1.1).

1.1.3 Nanoscale Systems Are on the Right Scale for Nanomedicine

It is important to have tools on the proper scale for the job. Nanomedicine, as single-cell medicine, requires that the tools be smaller than the objects (i.e., single cells) they are dealing with, as shown by this classic nanomedicine size scale (Figure 1.2).

Atom-by-atom assembly, or “nanomanufacturing,” still has some issues in terms of speed and practicality, but many nanostructures in biology use the laws of thermodynamics for “self-assembly.” The concept of nanotechnology was first mentioned by Nobel Laureate Richard Feynman, who in his famous 1959 “nanotechnology” lecture “Plenty of Room at the Bottom” proposed that atom-by-atom assembly of materials might someday be possible (Feynman, 1960). Many people think that “molecular manufacturing” proposed by futurist Eric Drexler in his 1991 MIT PhD dissertation is science fiction. Unlike conventional chemical batch synthesis of finished products from raw materials, molecular manufacturing would create products in an atom-by-atom assembly in a form of desktop manufacturing (Drexler, 1991). As of 2021, this has not yet been accomplished to the degree of real molecular manufacturing, as envisioned by Drexler and others (Figure 1.3).

Due to its controversial status, Drexler’s molecular manufacturing was overtly removed, perhaps unfairly, from the National Nanotechnology Initiative passed by Congress and signed into law in 2001. The original law sunset in 2008 and has not been formally renewed (Sargent, 2010). But Drexler’s molecular manufacturing is a topic that will probably not go away, nor should it. If it were indeed possible, it would revolutionize manufacturing as we know it, giving us a form of “3D atomic printing” that would be the nanotechnology equivalent of current 3D printing (Figure 1.4).

Figure 1.1 The old paradigm for most of the past few thousand years of human endeavors has been to “sculpt” larger objects into smaller objects: sculpture of Aphrodite (a) (source: www.ancientsculpture.net/images/products/small/252.jpg). The new paradigm of nanotechnology inverts this top-down process to a bottom-up approach (b), assembling nanomaterials atom by atom, as shown in (c), whereby 36 cobalt atoms are arranged in a “quantum corral” (source: www.aip.org/png/html/mirage.html).

Source: Leary (2010)
A strand of DNA is ~2 nm wide.

~5 million red blood cells in a drop of blood.

A 6' man is 1.62 meters tall or 2 billion nanometers.

1 mm (head of a pin)

300 μm (dust mite)

~2–5 μm wide

~5 million red blood cells in a drop of blood.

Figure 1.2 As shown in this “nanoscale” figure, nanomedicine tools must be smaller than a human cell so that single-cell treatments are possible.

3.6 nm (Channel)
DNA
Hexamer RNA
Connector

Figure 1.3 (a) The original concept of nanomanufacturing, as envisioned by Eric Drexler, is that one would need tiny machines capable of positioning atoms one at a time (source: http://metamodern.com/2009/02/27/high-throughput-nanomanufacturing). This challenging paradigm has yet to be fully realized, although there are a number of researchers attempting it. (b) The reality is that most nanomanufacturing will be done by thermodynamically driven self-assembly, in the same way that nature makes nanostructures such as Phi-29 RNA nanomotor structures (source: http://nihroadmap.nih.gov/nanomedicine/devcenters/phi29dnapackagingmotor.asp).

Figure 1.4 In a rather heated series of back-and-forth debates, Eric Drexler and Richard Smalley argued about the feasibility of molecular manufacturing. Smalley contended that it was impossible due to the inability to pick up and position atoms quickly enough, whereas Drexler countered that smaller components could self-assemble and then be positioned as larger pieces later in the process.

Source: Leary teaching
However, quite independently of science fiction, nanomanufacturing has been going on in the biological world for many millions or even billions of years. There are numerous nanomanufactured structures in biological organisms that perform nanomanufacturing of self-assembling structures quite naturally through the laws of thermodynamics. Self-assembling nanostructures, including a wide variety of nanoparticles of diverse compositions, are being nanomanufactured by thermodynamically driven self-assembly in many laboratories, including those of this author, around the world these days (cf. reviews: Haglund, Seale, and Leary, 2009; Leary, 2019; Seale and Leary, 2009). Indeed, our own bodies are full of self-assembling, nanomanufactured components, and viruses are truly one of nature’s self-manufacturing and self-assembling nanoparticle structures. Interestingly, these naturally occurring viral nanoparticles have also evolved over the millennia into a form of “nanomachines” that quite efficiently use host cell machinery to manufacture nanoparticle subcomponents for later self-assembly during the replication process. Through biomimicry (Benyus, 1997), nature inspires some of us to learn how to design synthetic nanoparticles, mimicking viruses, that do not replicate for their own purposes but rather to manufacture molecules therapeutic against a wide variety of diseases, as described in more detail later in this book. These “smart nanoparticles” are an important part of a new drug-device strategy (Figure 1.5).

**Figure 1.5** “Smart” nanoparticles capable of both diagnostics and therapeutics will allow a new stage of “theranostics” in modern medicine. 
Source: Leary teaching
1.2 The Progression of Medicine

The field of medicine has steadily progressed, particularly over the past 150 years with the discovery of disease pathogens, the importance of sterility in surgical interventions, the development of antimicrobials and vaccines, in vivo imaging, and a general embrace of new technologies. Nanotechnology just represents the next major technology to be applied to medicine. But its application will represent a fundamental paradigm shift from organ-level disease treatments to single-cell treatments. One area of medicine that has embraced nanomedicine concepts is ophthalmology (Zarbin et al., 2010a, 2010b, 2011, 2012).

1.2.1 Human Disease Really Happens at a Single-Cell Level

Human disease happens at a single-cell level, but we typically only define and treat disease when it affects the organ. We need a paradigm shift in our thinking if we are to fully understand and appreciate the power and promise of nanomedicine. We need to start thinking about human disease at a more fundamental and presymptomatic level. Indeed, if we are to be more forward-thinking and start understanding human disease in terms of regenerative medicine, or treating disease at an earlier presymptomatic single-cell level, we will need to move our thinking to abnormal changes happening within individual cells rather than macroscopic changes at the organ level. The purpose of medicine must become the way to keep people healthy and not allow them to become diseased. That will require fundamental changes in the ways we train doctors – to get them to think in terms of single-cell molecular biology and how to intervene at the single-cell level to keep patients healthy. By the time a patient manifests disease at the organ level, the disease may have already caused irreversible damage. We must also change our thinking about aging and start thinking about aging as not natural but rather the accumulation of unrepaired damage at the single-cell level. While that may appear too expensive a process, it is cheaper to repair damage at the early stages rather than waiting until extensive organ damage occurs. However, for this to happen – namely, medical interdiction at very early stages of disease – there must be molecular diagnostics at a presymptomatic stage of disease. Current healthcare practice and economics preclude this approach due to a failure to take into account the total bottom line in healthcare costs. Until that attitude changes, we will continue to ignore disease at the early stage when it is comparatively inexpensive to treat and then spend huge amounts of money later when the disease has progressed to a serious or even life-threatening stage – a case of bad healthcare economics!

1.2.2 Conventional “Modern” Medicine

Conventional medicine has progressed from fairly primitive surgical methods including “exploratory surgery” to today’s more sophisticated and noninvasive in vivo imaging by simple X-rays, CT scans, MRI scans, and PET scans followed by
minimally invasive laparoscopic surgery and even robotic-aided microsurgery. But with the exception of a limited number of targeted antibody therapies for specific cancers, drug therapy remains mostly untargeted drugs by either intravenous or oral administration. This has led to a crisis in the pharmaceutical industry whereby the number of drugs approved by the FDA each year has gone down drastically in the past 15 years while the cost of development has more than quadrupled. It is an unsustainable model. An easy initial partial fix to this problem is to repackage existing FDA-approved drugs into nano packages with targeted delivery and increased circulation times not only to enhance effectiveness but also to reduce side effects that can seriously affect patient health and well-being. We also need to incorporate individual genomics to know which drugs should not be administered to specific persons. This would be a huge advance for the pharmaceutical industry and lower their risk in development of new drugs. If you can exclude the people who would have severely adverse effects, beyond unpleasant side effects, many more drugs would be available for the rest of us!

1.2.3 “Personalized” or “Molecular” Medicine

There are essentially two main problems with our current approach to medicine. First, there are many very good drugs that cannot be used due to the extreme side effects, including death, in a subset of patients. Without patient-specific predictive information to tell us which patients should not receive specific drugs, we end up excluding these drugs from their effective use in the majority of patients. There is no way to win this game based on “population medicine.” The only way to win the game is to practice individual or personalized medicine. Now that we have the genomes of tens of thousands of individual human beings sequenced, we can start to use that information to decide which drugs to give, or not to give, to individual human beings. This will allow us to include many drugs that are good and appropriate for most people, but perhaps deleterious or even lethal to some people. That advance will totally change the drug industry and make drugs more affordable by avoiding the very large and expensive clinical trials which will become largely unnecessary. These large clinical study sizes are a result of us playing a game of Russian roulette with enough people sampled to start seeing the outlier patients. That is ultimately a poor way to test new drugs. We need a greater understanding of the causes of adverse side effects based on information from individual human genomes and also modeling of the differing biochemistry and metabolism of individual humans.

This problem will be gradually overcome when we have enough specific genome information for each patient to allow us to distinguish which patients should, or should not, receive specific drugs. Some of this can be done through rapid testing of specific portions of the individual patient genome through single nucleotide polymorphism (SNP) chips that examine the DNA variations in specific genes from individual to individual. But some of this work will be difficult and slow going, particularly with multigene disorders, and we will ultimately need to use whole genome information for each individual.
1.2.4 Nanomedicine “Single-Cell” Medicine

Personalized medicine will solve only part of the problem. That still leaves the serious problem of untargeted drug delivery whereby those drugs go everywhere in a patient’s body and cause unintended damage to other tissues and organs as part of the processes we refer to as side effects or, medically speaking, contraindications.

Nanomedicine is the process of treating the body, especially at a single-cell level, using nanodelivery systems to improve the targeting of drug/gene therapies to specific desired cells and to allow much smaller amounts of drugs to be put into the body in the first place. Clearly, by lowering the amount of drug needed by tenfold or a hundredfold, we are going to make a lot of progress in lessening side effects and dangerous patient outcomes. Paying attention to the design of nanomedical systems that have long circulation times in vivo is perhaps as important as targeting. The future of medicine lies in the combination of both personalized medicine and nanomedicine (Leary, 2010) (Figure 1.6).

Figure 1.6 (a) Conventional medicine still mostly uses hand-guided surgery (source: www.texasheartinstitute.org/HIC/Topics/images/ordome.jpg), with some robot-guided microsurgery. (b) The future of medicine will combine the capabilities of "personalized medicine" using pharmacogenomics based on the individual patient’s genome (source: http://ehp.niehs.nih.gov/tmg/members/2003/111-11/focus/focus.html). (c) Nanomedicine will work in close relation with "personalized medicine to provide superb targeting and drug delivery capabilities" or provide for real-time fluorescence-guided surgery to better see tumor margins. Source: Leary (2010)
1.3 How Conventional Medicine Works for Diagnosis of Disease

Conventional medicine works in a series of well-defined steps initiated upon the development of patient symptoms. The following six steps should be familiar to anyone navigating the current medical care system.

1.3.1 Identification of the “Diseased State”

The first step is the identification of a “diseased state” by a patient who “doesn’t feel right or well” and then goes or is taken to a clinic or a hospital emergency room. This initial self-diagnosis by the patient is highly subjective and based on symptoms that are hard to distinguish between different medical problems.

1.3.2 Collection of Medical Data by Health Professionals

The second step begins with attempts by nurses and doctors to collect simple measurements (e.g., temperature, blood pressure, heartbeat rate, palpitation to find “where it hurts” and/or any abnormal lump). By the time these measurements are taken, the disease may have become quite advanced. In addition, measurements taken in the doctor’s office at a single time point are a poor substitute for continuous measurements taken over days, weeks, or months.

1.3.3 Analysis of Initial Medical Data on Patient

This is followed by a third step whereby clinical tests (e.g., blood chemistry; urine chemical analysis; blood, urine, or sputum cultures to detect abnormal numbers or types of microbes; blood cell numbers and percentages by cell subpopulation types; biopsies of tissues and their interpretation by histopathologists) are administered to try to narrow down the disease diagnosis possibilities.

1.3.4 More Advanced Examinations of the Patient

The previous step is often followed by internal examinations using noninvasive imaging, such as standard x-rays, computerized tomography (CT) scans, magnetic resonance imaging (MRI) scans, and positron emission tomography (PET) functional imaging. Before the advent of modern noninvasive imaging methods, the patient was literally opened (i.e., exploratory surgery) by a surgeon. But due to the extreme invasiveness and the risk of infection, this is seldom done anymore. It should be seen only in cases where noninvasive diagnostics fail to diagnose the disease.

1.3.5 Comparison of Patient Data with “Normal” Ranges

In almost all cases, individual results are compared with the “normal” ranges of individuals thought not to be diseased. This step brings home the point that we are