Chapter 1
Introduction

Nanomedicine

Nanomedicine is defined as the application of nanobiotechnology to medicine. Its broad scope covers the use of nanoparticles and nanodevices in healthcare for diagnosis as well as therapeutics. Safety, ethical, and regulatory issues are also included.

Basics of Nanobiotechnology

Nanotechnology (Greek word nano means dwarf) is the creation and utilization of materials, devices, and systems through the control of matter on the nanometer-length scale, i.e., at the level of atoms, molecules, and supramolecular structures. Nanotechnology, as defined by the National Nanotechnology Initiative (http://www.nano.gov/), is the understanding and control of matter at dimensions of roughly 1–100 nm, where unique phenomena enable novel applications. Encompassing nanoscale science, engineering, and technology, nanotechnology involves imaging, measuring, modeling, and manipulating matter at this length scale. It is the popular term for the construction and utilization of functional structures with at least one characteristic dimension measured in nanometers – a nanometer is one billionth of a meter (10^{-9} m). This is roughly four times the diameter of an individual atom, and the bond between two individual atoms is 0.15 nm long. Proteins are 1–20 nm in size. The definition of "small," another term used in relation to nanotechnology, depends on the application but can range from 1 nm to 1 mm. Nano is not the smallest scale; further down the power of 10 are angstrom (=0.1 nm), pico, femto, atto, and zepto. By weight, the mass of a small virus is about 10 attograms. An attogram is one-thousandth of a femtogram, which is one-thousandth of a picogram, which is one-thousandth of a nanogram. Dimensions of various objects in nanoscale are shown in Table 1.1.

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Table 1.1 Dimensions of various objects in nanoscale

Object	Dimension (nm)
Width of a hair	50,000
Red blood cell	2,500
Vesicle in a cell	200
Bacterium	1,000
Virus	100
Exosomes (nanovesicles shed by dendritic cells)	65–100
Width of DNA	2.5
Ribosome	2–4
A base pair in human genome	0.4
Proteins	1–20
Amino acid (e.g., tryptophan, the largest)	1.2 (longest measurement)
Aspirin molecule	1
An individual atom	0.25

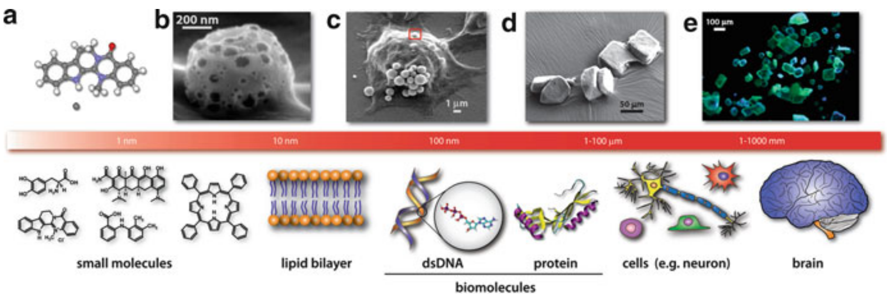

Fig. 1.1 Sizes of biologically entities relevant to the brain. (*Top row above scale bar*) From left to right: (**a**) X-ray crystal structure of Alzheimer's disease candidate drug, dehydroevodiamine HCl (DHED); (**b** and **c**) porous metal oxide microspheres being endocytosed by BV2 microglia cell (close-up and low magnification) SEM images; (**d** and **e**) SEM and fluorescence micrograph of DHED microcrystals (DHED is blue-green luminescent). (*Bottom row below the scale bar*) Left to right: small molecules, such as dopamine, minocycline, mefenamic acid, DHED, and heme, are ~1 nm or smaller. The lipid bilayer is a few nanometers thick. Biomolecules such as a microRNA and a protein are only a few nanometers in size. A single cell or neuron is tens or hundreds of microns in size. Size of human brain is tens of centimeters (Reproduced from: Suh WH, et al. Prog Neurobiol 2009;87:133–70 (by permission))

Given the inherent nanoscale functional components of living cells, it was inevitable that nanotechnology will be applied in biotechnology giving rise to the term nanobiotechnology. A brief introduction will be given to basic nanotechnologies from physics and chemistry, which are now being integrated into molecular biology to advance the field of nanobiotechnology. The aim is to understand the biological processes to improve diagnosis and treatment of diseases. Sizes of biologically entities relevant to the brain are shown in Fig. 1.1.

Relation of Nanobiotechnology to Nanomedicine

Technical achievements in nanotechnology are being applied to improve drug discovery, drug delivery, and pharmaceutical manufacturing. A vast range of applications have spawned many new terms, which are defined as they are described in various chapters. Numerous applications in the pharmaceutical industry can also be covered under the term "nanobiopharmaceuticals."

Landmarks in the Evolution of Nanomedicine

Historical landmarks in the evolution of nanomedicine are shown in Table 1.2.

Table 1.2 Historical landmarks in the evolution of nanomedicine

Year	Landmark
1905	Einstein published a paper that estimated the diameter of a sugar molecule at about 1 nm
1931	Max Knoll and Ernst Ruska discover the electron microscope – enables subnanomolar imaging
1959	Nobel Laureate Richard Feynman gave a lecture entitled "There's plenty of room at the bottom" at the annual meeting of the American Physical Society. He outlined the principle of manipulating individual atoms using larger machines to manufacture increasingly smaller machines (Feynman 1992)
1974	Start of development of molecular electronics by Aviram and Rattner (Hush 2003)
1974	Norio Taniguchi of Japan coined the word "nanotechnology"
1979	Colloidal gold nanoparticles used as electron-dense probes in electron microscopy and immunocytochemistry (Batten and Hopkins 1979)
1981	Conception of the idea of designing molecular machines analogous to enzymes and ribosomes (Drexler 1981)
1984	The first description the term dendrimer and the method of preparation of poly(amidoamine) dendrimers (Tomalia et al. 1985)
1985	Discovery of buckyballs (fullerenes) by Robert Curl, Richard Smalley, and Harold Kroto, which led to the award of Nobel Prize for chemistry in 1996 (Smalley 1985; Curl et al. 1997)
1987	Publication of the visionary book on nanotechnology potential "Engines of Creation" (Drexler 1987)
1988	Maturation of the field of supramolecular chemistry relevant to nanotechnology: construction of artificial molecules that interact with each other leading to award of the Nobel prize (Lehn 1988)
1990	Atoms visualized by the scanning tunneling microscope discovered in 1980s at the IBM Zürich Laboratory (Zürich, Switzerland), which led to award of a Nobel prize (Eigler and Schweizer 1990)
1991	Discovery of carbon nanotubes (Iijima et al. 1992)
1992	Principles of chemistry applied to the bottom-up synthesis of nanomaterials (Ozin 1992)
1994	Nanoparticle-based drug delivery (Kreuter 1994)
1995	FDA approved Doxil, a liposomal formulation of doxorubicin, as an intravenous chemotherapy agent for Kaposi's sarcoma. Drug carried by nanosize liposomes is less toxic with targeted delivery

(continued)

Table 1.2 (continued)

Year	Landmark
1997	Cancer targeting with nanoparticles coated with monoclonal antibodies (Douglas et al. 1997)
1997	Founding of the first molecular nanotechnology company – Zyvex Corporation
1998	First use of nanocrystals as biological labels, which were shown to be superior to existing fluorophores (Bruchez et al. 1998)
1998	Use of DNA-gelatin nanospheres for controlled gene delivery (Truong-Le et al. 1998)
1998	Use of the term "nanomedicine" in publications (Freitas 1998)
2000	Nanotechnology Initiative announced in the USA (Roco 2003)
2000	First FDA approval of a product incorporating the NanoCrystal® technology (Elan), solid-dose formulation of the immunosuppressant sirolimus – Rapamune® (Wyeth)
2003	Concept for nanolaser was developed at Georgia State University using nanospheres and nanolens system (Li et al. 2003)
2003	The US Senate passed the Nanotechnology Research and Development Act making the National Nanotechnology Initiative into law and authorized $3.7 billion over the next 4 years for the program
2005	FDA approved Abraxane™, a taxane based on nanotechnology, for the treatment of breast cancer. Nanoparticle form of the drug overcomes insolubility problems encountered with paclitaxel and avoids the use of toxic solvents

Nanomedicine as a Part of Evolution of Medicine

Medicine is constantly evolving, and new technologies are incorporated into the diagnosis and treatment of patients. This process is sometimes slow, and there can be a gap of years before new technologies are integrated in medical practice. The reasons for the delay are:

- Establishing the safety and efficacy of innovative treatments is a long process, particularly with clinical trials and regulatory reviews.
- The current generation of medical practitioners are still not well oriented toward biotechnology, and conservative elements of the profession may be slow in accepting and learning about nanobiotechnology, which is at the cutting edge of biotechnology.
- High cost of new technologies is a concern for the healthcare providers. Cost-benefit studies are needed to convince the skeptics that some of the new technologies may actually reduce the overall cost of healthcare.

Molecular medicine is already a recognized term. It should not be considered a subspecialty of medicine as molecular technologies would have an overall impact on the evolution of medicine. Recognition of the usefulness of biotechnology has enabled progress in the concept of personalized medicine, which again is not a branch of medicine but simply indicates a trend in healthcare and simply means the prescription of specific treatments and therapeutics best suited for an individual (Jain 2009). Various nanomachines and other nano-objects that are currently under investigation in medical research and diagnostics will soon find applications in the practice of medicine. Nanobiotechnologies are being used to create and study

Table 1.3 Nanomedicine in the twenty-first century

Nanodiagnostics
Extending limits of detection by refining currently available molecular diagnostic technologies
Development of new nanotechnology-based assays
Nanobiosensors
Nanoendoscopy
Nanoimaging
Nanopharmaceuticals
Nanoparticulate formulations of drugs
Nanotechnology-based drug discovery
Nanotechnology-based drug delivery
Regenerative medicine
Use of nanotechnology for tissue engineering
Transplantation medicine
Exosomes from donor dendritic cells for drug-free organ transplants
Nanomedicine specialties
Nanocardiology
Nanodermatology
Nanodentistry
Nanogerontology
Nanohematology
Nanoimmunology
Nanomicrobiology
Nanonephrology
Nanoneurology
Nanooncology
Nanoophthalmology
Nanoorthopedics
Implants
Bioimplantable sensors that bridge the gap between electronic and neurological circuitry
Durable rejection-resistant artificial tissues and organs
Implantations of nanocoated stents in coronary arteries to elute drugs and to prevent reocclusion
Implantation of nanoelectrodes in the brain for functional neurosurgery
Implantation of nanopumps for drug delivery
Nanosurgery
Minimally invasive surgery: miniaturized nanosensors implanted in catheters to provide real-time data
Nanosurgery by integration of nanoparticles and external energy
Nanorobotic treatments
Vascular surgery by nanorobots introduced into the vascular system
Nanorobots for detection and destruction of cancer

models of human disease, particularly immune disorders. Introduction of nanobiotechnologies in medicine will not create a separate branch of medicine but simply implies improvement of diagnosis as well as therapy.

Current research is exploring the fabrication of designed nanostructures, nanomotors, microscopic energy sources, and nanocomputers at the molecular scale, along with the means to assemble them into larger systems, economically and in great numbers. Some of the applications of nanobiotechnology in medicine are shown in Table 1.3.