BIOMEDICAL NANOTECHNOLOGY

Edited by
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Preface

In this book, we present the state of the art of nanotechnology research intended for applications in biomedical technologies in three subfields: nanodrugs and drug delivery inside the body; prostheses and implants; and diagnostics and screening technologies for laboratory use. For each of these three subfields, we explore the relevant developments in research.

Nanoparticles such as nanotubes and quantum dots are increasingly applied as drug delivery vehicles. Applications may include gene therapy, cancer treatments, and treatments for HIV and other diseases for which no cures presently exist. Implanted drug delivery or monitoring devices can also include nanostructured materials. Prostheses and implants include nanostructured materials. For example, hip replacements can be made to fit better into the body if coated with nanostructured materials. Nerve tissue can be made to grow along small silicon structures, and this may help paralyzed patients. Nanotechnologies may also contribute to electronic eyes and ears. The research on implants and prostheses focuses on two main directions: (1) biological nanostructures that put biological molecules and tissues in a strait jacket to grow into new structures and (2) biomimetic nanotechnology that starts with physical and chemical structures and aims for a completely new material.

Diagnostics and screening technologies include cantilever biochemical sensors, different types of scanning probe microscopes, lab-on-a-chip techniques, and biosensors. Nanoscience and nanotechnology focus on connecting living materials and electronics as well as on imaging and manipulating individual molecules.

We place these developments in social and economic contexts to assess the likelihood of uptake of these technologies and their relevance to the world's most pressing health needs. Do real needs and markets exist for these devices? We also include a chapter exploring potential risks. The developments in the life science technologies involving GMOs, cloning, and stem cell research have shown that unexpected public concern may slow acceptance of new technologies. For nanotechnology, the public debate is just emerging. Researchers, government officials, and industrialists are actively attempting to assess the risks and redirect research toward the technologies consumers want and away from what the public will not accept.

The scope of this book includes scientific and technological details along with detailed discussions of social and economic contexts. The intended audience includes researchers active in nanoscience and technology in industry and academia, medical professionals, government officials responsible for research, innovation, health care, and biodefense, industrialists in pharmaceutical and biomedical technology, nongovernmental organizations interested in environmental, health care, or peace issues, students, and interested lay persons. We assume readers have academic training, but no expertise in nanotechnology.

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Introduction

Converging Technologies: Nanotechnology and Biomedicine

Mihail C. Roco

Recent research on biosystems at the nanoscale has created one of the most dynamic interdisciplinary research and application domains for human discovery and innovation (Figure I.1).* This domain includes better understanding and treatment of living and thinking systems, revolutionary biotechnology processes, synthesis of new drugs and their targeted delivery, regenerative medicine, neuromorphic engineering, and biocompatible materials for sustainable environment. Nanobiosystems and biomedical research are priorities in the United States, the European Union, the United Kingdom, Australia, Japan, Switzerland, China, and other countries and regional organizations.

With proper attention to ethical issues and societal needs, these converging technologies could yield tremendous improvements in human capabilities, societal outcomes, and the quality of life. The worldwide emergence of nanoscale science

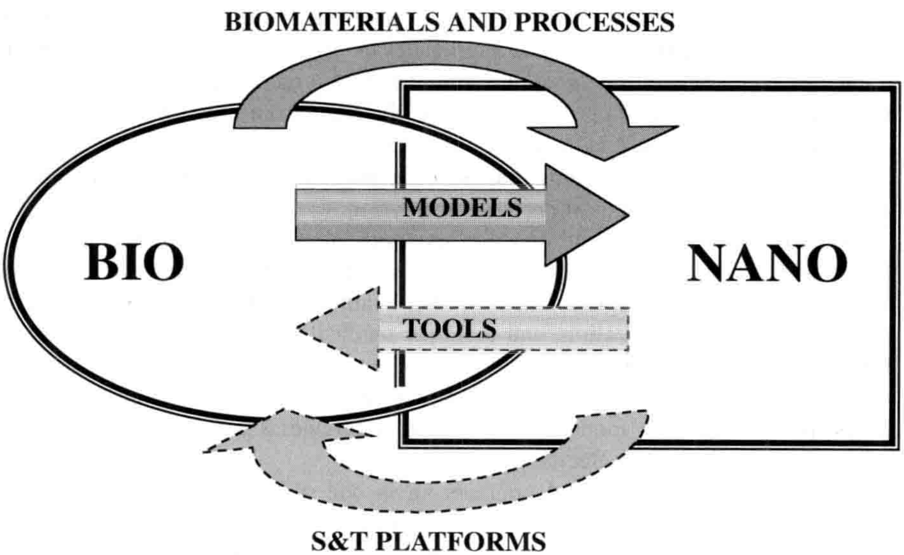

Figure I.1 Interactions of biology and nanotechnology.

* The views expressed in this chapter are those of the author and not necessarily those of the U.S. National Science and Technology Council or the National Science Foundation.

and engineering was marked by the announcement of the U.S. National Nanotechnology Initiative (NNI) in January 2000. Its relevance to biomedicine is expected to increase rapidly in the future. The contributions made in this volume are outlined in the context of research directions for the field.

NANOTECHNOLOGY AND NANOBIOMEDICINE

Nanotechnology is the ability to measure, design, and manipulate at the atomic, molecular and supramolecular levels on a scale of about 1 to 100 nm in an effort to understand, create, and use material structures, devices, and systems with fundamentally new properties and functions attributable to their small structures.[1] All biological and man-made systems have their first levels of organization at the nanoscale (nanocrystals, nanotubes, and nanobiomotors), where their fundamental properties and functions are defined. The goal in nanotechnology may be described as the ability to assemble molecules into useful objects hierarchically integrated along several length scales and then, after use, disassemble objects into molecules. Nature already accomplishes this in living systems and in the environment.

Rearranging matter on the nanoscale using "weak" molecular interactions such as van der Waals forces, H bonds, electrostatic dipoles, fluidics, and various surface forces requires low energy consumption and allows for reversible and other subsequent changes. Such changes of usually "soft" nanostructures in a limited temperature range are essential for bioprocesses to take place. Research on "dry" nanostructures is now seeking systematic approaches to engineering human-made objects at nanoscale and integrating nanoscale structures into large-scale structures as nature does. While the specific approaches may be different from the slow evolutions of living systems in aqueous media, many concepts such as self-assembling, templating, interaction on surfaces of various shapes, self-repairing, and integration on multiple length scales can be used as sources of inspiration.

Nanobiomedicine is a field that applies nanoscale principles and techniques to understanding and transforming inert materials and biosystems (nonliving, living or thinking) for medical purposes such as drug synthesis, brain understanding, body part replacement, visualization, and tools for medical interventions. Integration of nanotechnology with biomedicine and biology, and with information technology and cognitive science is expected to accelerate in the next decade.[2] Convergence of nanoscale science with modern biology and medicine is a trend that should be reflected in science policy decisions.[3]

Nanobiosystem science and engineering is one of the most challenging and fastest growing components of nanotechnology. It is essential for better understanding of living systems and for developing new tools for medicine and solutions for health care (such as synthesis of new drugs and their targeted delivery, regenerative medicine, and neuromorphic engineering). One important challenge is understanding the processes inside cells and neural systems. Nanobiosystems are sources of inspiration and provide models for man-made nanosystems. Research may lead to better biocompatible materials and nanobiomaterials for industrial applications. The confluence of biology and nanoscience will contribute to unifying concepts of science, engineering, technology, medicine, and agriculture.

TOWARD MOLECULAR MEDICINE

Nanotechnology provides investigation tools and technology platforms for biomedicine. Examples include working in the subcellular environment, investigating and transforming nanobiosystems (for example, the nervous system) rather than individual nanocomponents, and developing new nanobiosensor platforms. Investigative methods of nanotechnology have made inroads in uncovering fundamental biological processes, including self-assembling, subcellular processes, and system biology (for example, the biology of the neural system).

Key advancements have been made in measurements at the molecular and subcellular levels and in understanding the cell as a highly organized molecular mechanism based on its abilities of information utilization, self-organization, self-repair, and self-replication.[4] Single molecule measurements are shedding light on the dynamic and mechanistic properties of molecular biomachines, both *in vivo* and *in vitro*, allowing direct investigation of molecular motors, enzyme reactions, protein dynamics, DNA transcription, and cell signaling. Chemical composition has been measured within a cell *in vivo*.

Another trend is the transition from understanding and control of a single nanostructure to nanosystems. We are beginning to understand the interactions of subcellular components and the molecular origins of diseases. This has implications in the areas of medical diagnostics, treatments, and human tissue replacements. Spatial and temporal interactions of cells including intracellular forces have been measured. Atomic force microscopy has been used to measure intermolecular binding strength of a pair of molecules in a physiological solution, providing quantitative evidence of their cohesive function.[5] Flows and forces around cells have been quantitatively determined, and mechanics of biomolecules are better understood.[6] It is accepted that cell architecture and macro behavior are determined by small-scale intercellular interactions.

Other trends include the ability to detect molecular phenomena and build sensors and systems of sensors that have high degrees of accuracy and cover large domains. Fluorescent semiconductor nanoparticles or quantum dots can be used in imaging as markers for biological processes because they photobleach much more slowly than dye molecules and their emission wave lengths can be finely tuned. Key challenges are the encapsulation of nanoparticles with biocompatible layers and avoiding nonspecific adsorption. Nanoscience investigative tools help us understand self-organization, supramolecular chemistry and assembly dynamics, and self-assembly of nanoscopic, mesoscopic, and even macroscopic components of living systems.[7]

Emerging areas include developing realistic molecular modeling for "soft" matter,[8] obtaining nonensemble-averaged information at the nanoscale, understanding energy supply and conversion to cells (photons and lasers), and regeneration mechanisms. Because the first level of organization of all living systems is at the nanoscale, it is expected that nanotechnology will affect almost all branches of medicine. This volume discusses important contributions in key areas. In Chapter 1, Morrison and Malsch discuss worldwide trends in biomedical nanotechnology programs. They cover the efforts of governments, academia, research organizations, and other entities related to biomedical nanotechnology.

DRUG SYNTHESIS AND DELIVERY

Yamamoto (Chapter 2) discusses the new contributions of nanotechnology in comparison to existing methods to release, target, and control drug delivery inside the human body. Self-assembly and self-organization of matter offer new pathways for achieving desired properties and functions. Exploiting nanoparticle sizes and nanosized gaps between structures represent other ways of obtaining new properties and physical access inside tissues and cells. Quantum dots are used for visualization in drug delivery because of their fluorescence and ability to trace very small biological structures. The secondary effects of the new techniques include raising safety concerns such as toxicity that must be addressed before the techniques are used in medical practice.

IMPLANTS AND PROSTHESES

Van den Beucken et al. (Chapter 3) demonstrates how nanotechnology approaches for biocompatible implants and prostheses become more relevant as life expectancy increases. The main challenges are the synthesis of biocompatible materials, understanding and eventually controlling the biological processes that occur upon implantation of natural materials and synthetic devices, and identifying future applications of biomedical nanotechnology to address various health issues. The use of currently available nanofabrication methods for implants and understanding cell behavior when brought in contact with nanostructured materials are also described.

DIAGNOSTICS AND SCREENING

Del Campo and Bruce (Chapter 4) review the potential of nanotechnology for high throughput screening. The complexity and diversity of biomolecules and the range of external agents affecting biomolecules underline the importance of this capability. The current approaches and future trends are outlined for various groups of diseases, tissue lapping, and therapeutics. The most successful methods are based on flat surface and fiberoptic microarrays, microfluidics, and quantum dots.

Nanoscale sensors and their integration into biological and chemical detection devices for defense purposes are reviewed by Shipbaugh et al. (Chapter 5). Typical threats and solutions for measuring, networking, and transmitting information are presented. Airborne and contact exposures can be evaluated using nanoscale principles of operation for sensing. Key challenges for future research for biological and chemical detection are outlined.[8]

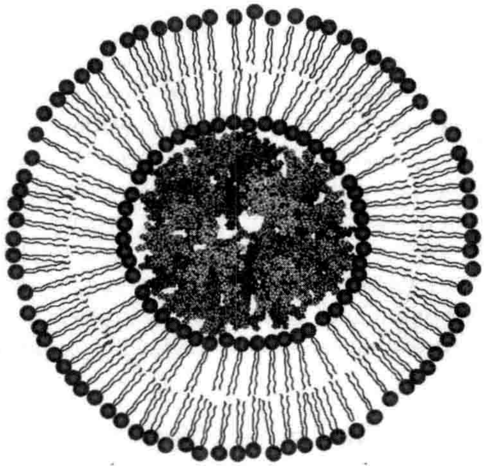

Figure I.2 Interactions of biological and synthetic materials. A generation 5 dendrimer wrapped in lipid bilayer removed from a cell. (From Baker, J. Direct observation of lipid bilayer disruption by dendrimers. Personal communication, 2004.)

One example of the complexity of the scientific issues identified at the interface between synthetic and biological materials and systems is the study of toxicity caused by dendrimers.[9] Generation 5 dendrimers of particular diameters and electrically and positively charged can actually rip lipid bilayers from cells to form micellar-like structures (Figure I.2), leading to cytotoxicity. The health concerns caused by nanotechnology products must receive full consideration from the private sector and government organizations because of the specific properties and types of complex interactions at the nanoscale.

NANOTECHNOLOGY PLATFORMS FOR BIOMEDICINE

Nanotechnology offers new solutions for the transformation of biosystems and provides a broad technological platform for applications in industry; such applications include bioprocessing, molecular medicine (detection and treatment of illnesses, body part replacement, regenerative medicine, nanoscale surgery, synthesis and targeted delivery of drugs), environmental improvement (mitigation of pollution and ecotoxicology), improving food and agricultural systems (enhancing agricultural output, new food products, food conservation), and improving human performance (enhancing sensorial capacity, connecting brain and mind, integrating neural systems with nanoelectronics and nanostructured materials).

Nanotechnology will also serve as a technological platform for new developments in biotechnology; for example, biochips, "green" manufacturing (biocompatibility and biocomplexity aspects), sensors for astronauts and soldiers, biofluidics for handling DNA and other molecules, *in vitro* fertilization for livestock, nanofiltration, bioprocessing by design, and traceability of genetically modified foods.

Exploratory areas include understanding, conditioning, and repairing brain and other parts for regaining cognition, pharmaceuticals and plant genomes, synthesis of more effective and biodegradable chemicals for agriculture, implantable detectors, and use of saliva instead of blood for detection of illnesses. Broader issues include economic molecular medicine, sustainable agriculture, conservation of biocomplexity, and enabling emerging technologies. Measurements of biological entities such as neural systems may be possible at the level of developing interneuronal synapse circuits and their 20-nm diameter synoptic vesicles. Other potential breakthroughs that may be targeted by the research community in the next 10 years are the detection and treatment of cancer, treatment of brain illnesses, understanding and addressing chronic illnesses, improving human sensorial capacity, maintaining quality of life throughout the aging process, and enhancing learning capabilities.

FUNDING AND POLICY IMPLICATIONS

With proper attention to ethical issues and societal needs, these converging technologies could allow tremendous improvements in human capabilities, societal outcomes, and the quality of life. Malsch (Chapter 6) examines the potential of nanotechnology to address health care needs and the societal implications of nanobiomedical research and development. The most important avenues of disease treatment and the main issues to be considered by governments, civic organizations, and the public are evaluated. The social, economic, ethical, and legal aspects are integral parts of nanotechnology R&D for biomedical applications.

Schuler (Chapter 7) reviews the potential risks of biomedical nanotechnology and outlines several scenarios for eventual regulation via market forces, extensions of current regulations, accidents, regulatory capture, self-regulation, or technology ban. The chances of success of these scenarios are determined by the way the stakeholders respond to the large-scale production and commercialization expected to begin within the next decade.

The United States initiated a multidisciplinary strategy for development of science and engineering fundamentals through its NNI in 2000. Japan and Europe now have broad programs and plans for the next 4 or 5 years. More than 40 countries have developed programs or focused projects in nanotechnology since 2000. Research on biosystems has received larger support in the United States, the United Kingdom, Germany, Switzerland, and Japan. Other significant investments in nanotechnology research programs with contributions to nanobiosystems have been made by the European Community, Australia, Taiwan, Canada, Finland, Italy, Israel, Singapore, and Sweden. Relatively large programs in nanotechnology but with small biosystems components until 2004 have been developed by South Korea and China. Worldwide government funding has increased to about eight times what it was in 1997, exceeding $3.6 billion in 2004 (see http://www.nsf.gov/nano). Differences among countries can be noted by the research domains they choose, the levels of program integration into various industrial sectors, and the time scales of their R&D targets.

Of the total NNI investment in 2004, about 15% is dedicated to nanobiosystems in two ways. First, the implementation plan of NNI focuses on fundamental research related to nanobiosystems and nanomedicine. Second, the program involves two grand challenges related to health issues and bionanodevices. Additional investments have been made for development of infrastructures at various NSF centers, including the Cornell University Nanotechnology Center and additional nanoscale science and engineering centers at Rice University, the University of Pennsylvania, and Ohio State University.

The NNI was evaluated by the National Research Council and the council published its findings in June 2002. One recommendation was to expand research at the interface of nanoscale technology with biology, biotechnology, and life sciences. Such plans to extend nanobiosystems research are under way at the U.S. Department of Energy (DOE), the National Institutes of Health (NIH), the National Science Foundation (NSF), and the Department of Agriculture (USDA). A NSF–Department of Commerce (DOC) report recommends a focus on improving physical and mental human performance through converging technologies.[2] The NSF, the National Aeronautics & Space Administration (NASA), and the Department of Defense (DOD) have included aspects of converging technologies and improving human performance in their program solicitations. The Defense Advanced Research Projects Agency (DARPA) instituted a program on engineered biomolecular nanodevices and systems. A letter sent to the NIH director by seven US senators in 2003 recommended that the NIH increase funding in nanotechnology. The White House budget request for fiscal 2004 lists "nanobiosystems for medical advances and new products" as a priority within the NNI. Nanobiotechnology RRD is highlighted in the long-term NNI Strategic Plan published in December 2004 (http://www.nano.gov). Public interactions provide feedback for the societal acceptance of nanotechnology, and particularly the aspects related to human dimensions and nanobiotechnology.[10,11]

Nanobiosystems is an area of interest recognized by various international studies on nanotechnology, such as those prepared by Asia-Pacific Economic Council (APEC),[12] the Meridian Institute,[13] and Economic Organization of Developed Countries (OECD).[14] In a survey performed by the United Kingdom Institute of Nanotechnology and by OECD,[14] experts identified the locations of the most sophisticated nanotechnology developments in the medical and pharmaceutical areas in the United States (48%), the United Kingdom (20%), Germany (17%), Switzerland (8%), Sweden (4%), and Japan (3%). The U.S. NNI plans to devote about 15% of its fiscal year 2004 budget to nanobiosystems; Germany will allocate about 10% and France about 8%. The biology route to nanotechnology may be a choice for countries with less developed economies because required research facility investments are lower.

CLOSING REMARKS

Nanoscale and biosystem research areas are merging with information technology and cognitive science, leading to completely new science and technology platforms in genome pharmaceuticals, biosystem-on-a-chip devices, regenerative medicine, neuroscience, and food systems. A key challenge is bringing together biologists and doctors with scientists and engineers interested in the new measurement and fabrication capabilities of nanotechnology. Another key challenge is forecasting and addressing possible unexpected consequences of the revolutionary systems and engineering developments utilized in nanobiosystems. Priority science and technology goals may be envisioned for international collaboration in nanoscale research and education, better comprehension of nature, increasing productivity, sustainable development, and addressing humanity and civilization issues.

The confluence of biology, medicine, and nanotechnology is reflected in government funding programs and science policies. For example, the U.S. NNI plans to increase its contributions to programs dedicated to nanobiosystems beyond the current level of about 15%; similar trends in other countries intended to better recognize nanobiosystems research have also been noted.

Nanoscale assemblies of organic and inorganic matter lead to the formation of cells and other activities of the most complex known systems — the human brain and body. Nanotechnology plays a key role in understanding these processes and the advancement of biological sciences, biotechnology, and medicine. Four chapters in this volume present key issues of molecular medicine, from drug delivery and biocompatible replacement body parts to devices and systems for high throughput diagnostics and biodefense. Three other chapters provide overviews on relevant research and development programs, the social and economic contexts, and potential uncertainties surrounding nanobiomedical developments. This broad perspective is of interest not only to the scientific and medical community, but also to science policy makers, social scientists, economists, and the public.

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CHAPTER 1

Trends in Biomedical Nanotechnology Programs Worldwide

Mark Morrison and Ineke Malsch

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