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Nanomedicine and Nanobiotechnology

Stergios Logothetidis

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《纳米科学与技术》丛书序

在新兴前沿领域的快速发展过程中，及时整理、归纳、出版前沿科学的系统性专著，一直是发达国家在国家层面上推动科学与技术发展的重要手段，是一个国家保持科学技术的领先权和引领作用的重要策略之一。

科学技术的发展和应用，离不开知识的传播：我们从事科学研究，得到了“数据”（论文），这只是“信息”。将相关的大量信息进行整理、分析，使之形成体系并付诸实践，才变成“知识”。信息和知识如果不能交流，就没有用处，所以需要“传播”（出版），这样才能被更多的人“应用”，被更有效地应用，被更准确地应用，知识才能产生更大的社会效益，国家才能在越来越高的水平上发展。所以，数据→信息→知识→传播→应用→效益→发展，这是科学技术推动社会发展的基本流程。其中，知识的传播，无疑具有桥梁的作用。

整个 20 世纪，我国在及时地编辑、归纳、出版各个领域的科学技术前沿的系列专著方面，已经大大地落后于科技发达国家，其中的原因有许多，我认为更主要的是缘于科学文化的习惯不同：中国科学家不习惯去花时间整理和梳理自己所从事的研究领域的知识，将其变成具有系统性的知识结构。所以，很多学科领域的第一本原创性“教科书”，大都来自欧美国家。当然，真正优秀的著作不仅需要花费时间和精力，更重要的是要有自己的学术思想以及对这个学科领域充分把握和高度概括的学术能力。

纳米科技已经成为 21 世纪前沿科学技术的代表领域之一，其对经济和社会发展所产生的潜在影响，已经成为全球关注的焦点。国际纯粹与应用化学联合会（IUPAC）会刊在 2006 年 12 月评论：“现在的发达国家如果不发展纳米科技，今后必将沦为第三世界发展中国家。”因此，世界各国，尤其是科技强国，都将发展纳米科技作为国家战略。

兴起于 20 世纪后期的纳米科技，给我国提供了与科技发达国家同步发展的良好机遇。目前，各国政府都在加大力度出版纳米科技领域的教材、专著以及科普读物。在我国，纳米科技领域尚没有一套能够系统、科学地展现纳米科学技术各个方面前沿进展的系统性专著。因此，国家纳米科学中心与科学出版社共同发起并组织出版《纳米科学与技术》，力求体现本领域出版读物的科学性、准确性和系统性，全面科学地阐述纳米科学技术前沿、基础和应用。本套丛书的出版以高质量、科学性、准确性、系统性、实用性为目标，将涵盖纳米科学技术的所有领域，全面介绍国内外纳米科学技术发展的前沿知识；并长期组织专家撰写、编辑出版下去，为我国

表面分子组装》，是对相关工作的归纳总结。

多年来，本人的研究组开展固体表面分子组装研究，不但发展表面组装方法，还一直试图找到分子结构-固体种类-组装结构间的关系，也不放过发现组装结构中重要现象的机会并阐明原因，意欲探索表面分子组装规律，利用分子组装实现表面功能化。书中在介绍固体表面的结构特点和 STM 技术等表面分子组装基础知识之后，顺序介绍了简单烷烃/烷烃衍生物分子的组装结构、复杂配合物分子的组装、主客体组装以及功能化组装等，随后介绍结构转化研究、手性结构研究、电化学环境下的组装和相变化，最后是可能的表面功能化，内容安排尽量承上启下、先易后难且逻辑相关。

借此机会，我要感谢我研究组的研究生们，他们倾心科学，随我多年耕耘于固体表面分子组装研究领域，努力工作，夜以继日，他们终学有所成，也留下了丰富的科研结果。陈婷、严会娟、殷雅侠、陈庆、张旭、崔博、管翠中、郑轻娜等还参与了书稿内容整理、文献核对等工作。感谢科学出版社杨震、张淑晓和刘冉诸位编辑的悉心指导，感谢国家出版基金对本书的出版资助。感谢国家自然科学基金委员会、科技部和中国科学院，多年来，我的研究工作一直得到他们的支持，本书中的研究内容大多是在他们的资助下获得的科研成果。

还要感谢我的妻子姜红，她不厌其烦地整理我写下的零散片段，帮助打字输入我的手写书稿，保存相关资料，愿本书的出版给她带去一份快乐！

分子组装研究历史已久，内容丰富，且时有挑战课题出现，也有轰动性和里程碑性成果问世。限于水平和时间，书中不妥之处在所难免，恳请各位前辈和同行不吝赐教。出版本书意在抛砖引玉，以诱导、鼓励更多的科技工作者，尤其是青年科技工作者加入该研究行列，发展新技术，探索规律，攻坚克难；同时，发现新问题和解决新问题，推动分子组装研究不断发展。

Preface

This book presents the state-of-the-art laboratory, scientific and clinical aspects of nanotechnologies, nanomaterials, and tools for medical applications. It gives a broad overview of nanomedical utilities in order to achieve breakthroughs in health care, ranging from nanoparticle drug delivery, diagnostics, regenerative medicine, nanomaterials for advanced medical implants, nanodentistry, and pharmaceutics to toxicity issues. The different pillars of the nanomedicine field are highlighted, in respect to clinical needs for the accurate diagnosis and effective treatment of human diseases. It also presents a spectra of nanoscale imaging modalities for hemocompatibility and cytotoxicity assessment of nanostructured materials implemented in the medical field. The authors, having a distinguished expertise in the academic and industrial world, take an interdisciplinary approach of medicine, biology, pharmacy, physics, chemistry, engineering, nanotechnology, and materials science, and as an outcome, this book will provide the cutting-edge data on nanomedicine, in a comprehensive and simple way. Thus, this book will be of great value to researchers, graduate students, and medical doctors who want to enhance their knowledge and expertise in the field of nanomedicine.

Thessaloniki, Greece
August 2011

Stergios Logothetidis

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Contents

Chapter 1
Nanomedicine: The Medicine of Tomorrow

S. Logothetidis

Abstract Nowadays nanotechnology has become a technological field with great potential since it can be applied in almost every aspect of modern life. One of the sectors where nanotechnology is expected to play a vital role is the field of medical science. The interaction of nanotechnology with medicine gave birth to a completely new scientific field called nanomedicine. Nanomedicine is a field that aims to use the nanotechnology tools and principles in order to improve human health in every possible way. Nanotechnology provides monitoring tools and technology platforms that can be used in terms of detection, diagnostic, bioanalysis and imaging. New nanoscale drug-delivery systems are constantly designed with different morphological and chemical characteristics and unique specificity against tumours, offering a less harmful approach alternative to chemo- and radiotherapies. Furthermore, nanotechnology has led to great breakthroughs in the field of tissue engineering, making the replacement of damaged tissues and organs a much feasible procedure. The thorough analysis of bio and non-bio interactions achieved by versatile nanotools is essential for the design and development of highly performed medical implants. The continuous revolution in nanotechnology will result in the fabrication of nanostructures with properties and functionalities that can benefit patient's physiology faster and more effectively than conventional medical procedures and protocols. The number of nanoscale therapeutical products is rapidly growing since more and more nanomedical designs are reaching the global market. However the nanotoxic impact that these designs can have on human health is an era that requires still more investigation. The development of specific guidance documents at a European level for the safety evaluation of nanotechnology products in medicine is strongly recommended and the need for further research in nanotoxicology is identified. Ethical and moral concerns also need to be addressed in parallel with the new developments.

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1.1 Introduction

Nanoscale is generally considered to be at a size below 0.1 μm or 100 nm (a nanometre is one billionth of a metre, 10^{-9} m). Nanoscale science (or nanoscience) studies the phenomena, properties and responses of materials at atomic, molecular and macromolecular scales, and in general at sizes between 1 and 100 nm. In this scale, and especially below 5 nm, the properties of matter differ significantly (i.e. quantum scale effects play an important role) from that at a larger particulate scale. Nanotechnology is then the design, the manipulation, the building, the production and the application, by controlling the shape and size, of the properties (responses) and functionality of structures, devices and systems of the order of less than 100 nm.

Nanotechnology is considered an emerging technology due to the possibility to advance well-established products and to create new products with totally new characteristics and functions with enormous potential in a wide range of applications. In addition to various industrial uses, great innovations are foreseen in information and communication technology, biology and biotechnology, medicine and medical technology, metrology, etc. It is anticipated that nanotechnology can have an enormous positive impact on human health. Relevant processes of living organisms occur basically at nanometre scale; elementary biological units such as DNA, proteins or cell membranes are of this dimension. By the means of nanotechnology, these biological units are going to be better comprehended so that they can be specifically guided or directed. Miniaturization down to nanometre scale provides to become an essential feature of biomedical products and procedures in postgenomic era. Nanoscale devices could be 100–10,000 times smaller than human cells but are similar in size to large biomolecules such as enzymes and receptors. Nanoscale devices smaller than 50 nm can easily enter most cells, and those smaller than 20 nm can move out of blood vessels as they circulate through the body.

Huge aspirations are coupled to nanotechnological developments in modern medicine (Nanotechnology, Biotechnology, Information Technology & Cognitive Science – *NBIC* developments). The potential medical applications are predominantly in diagnostics (disease diagnosis and imaging), monitoring, the availability of more durable and better prosthetics, and new drug-delivery systems for potentially harmful drugs [1, 2], as shown in Fig. 1.1. For example, nanoscale diagnostics are expected to identify in the becoming, giving the opportunity to intervene specifically prior to a symptomatically detected onset disease.

Biomedical nanotechnology presents revolutionary opportunities in the fight against many diseases. An area with near-term potential is detecting molecules associated with diseases such as cancer and diabetes mellitus, and neurodegenerative diseases, as well as detecting microorganisms and viruses associated with infections, such as pathogenic bacteria, fungi and HIV viruses. For example, in the field of cancer therapy, promising novel nanoparticles will respond to externally applied physical stimuli in ways that make them suitable therapeutics or therapeutic delivery systems. Another important field of application for nanotechnology

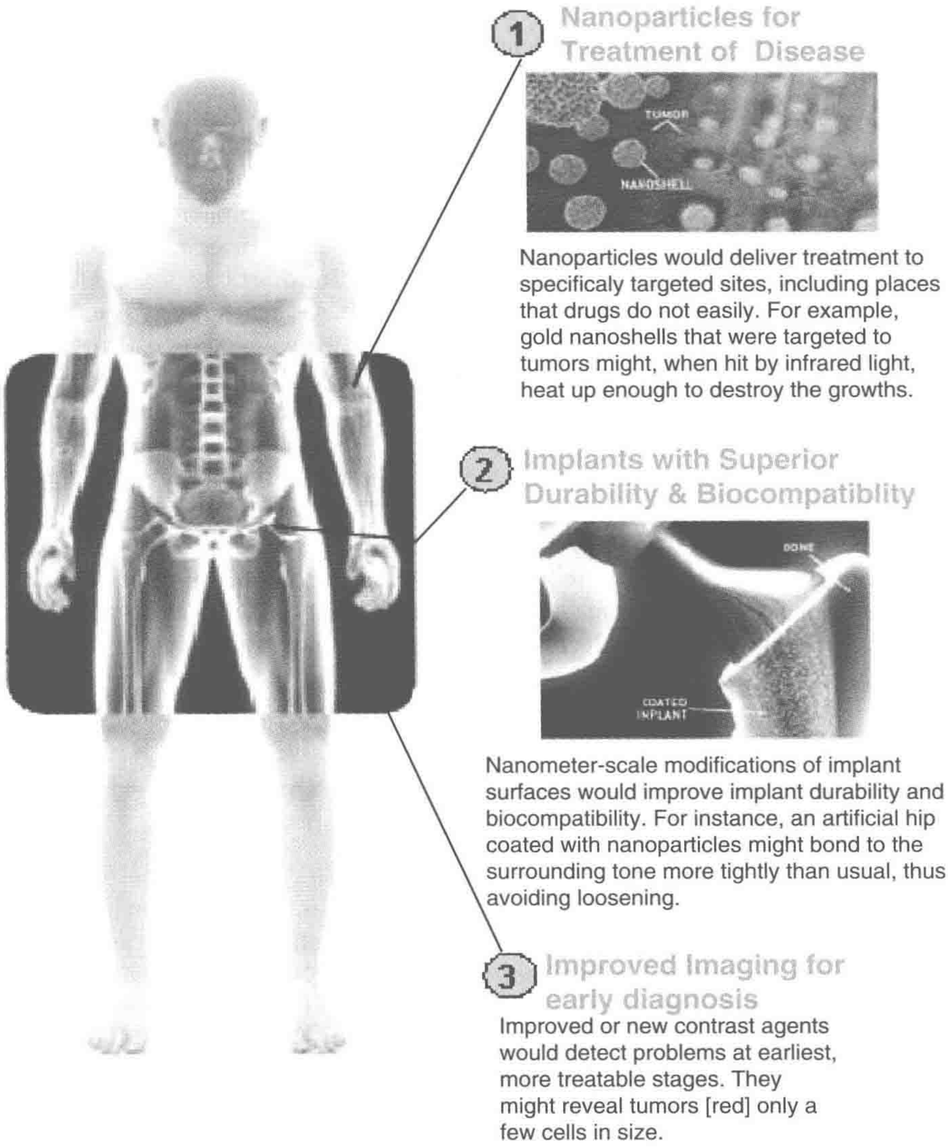

Fig. 1.1 Great developments are expected in medicine with the use of nanotechnology, such as (1) use of nanoparticles for the treatment of diseases, (2) implants with superior durability and biocompatibility and (3) improved imaging for early diagnosis

is biomaterials used, for example, in orthopaedic implants or as scaffolds for tissue-engineered products. Nanotechnology might yield nanostructured surfaces preventing non-specific protein adsorption. Control of surface properties at nanolevel was shown to increase the biocompatibility of the materials [3].

While products based on nanotechnology are actually reaching the market, sufficient knowledge on the associated toxicological risks is still lacking. Reducing the size of structures to nanolevel results in distinctly different properties. In addition to the chemical composition, which largely dictates the intrinsic toxic properties, very small size appears to be a dominant indicator for drastic or toxic effects of particles. From a regulatory point of view, a risk management strategy is already a requirement for all medical technology applications [2].

In order to discuss the advances of nanotechnology in modern medicine, we presented in Sect. 1.1 the terms and concepts of nanoscale and nanotechnology, and the relevant process and relation to living units. The impact of nanomaterials and nanoparticles in medicine is presented in Sect. 1.2, followed by a description of nanotechnology tools in medicine in Sect. 1.3. The impact of nanotechnology in medicine and medical technology is presented in Sect. 1.4, first with the introduction of nanomedicine and the "nanorobots", and then through some of myriad applications in diagnosis and treatment (such as biocompatibility and implants, cardiology, cancer, theranostics, etc.). In Sect. 1.5, a reference to the possible risks for human health is given.

1.2 Nanomaterials and Nanoparticles in Biomedical Applications

Novel nanomaterials and nanoparticles are envisaged to have a major impact on a number of different relevant areas. Materials with high performance and unique properties can be produced, which traditional synthesis and manufacturing methods could not create. Future nanoparticles should act as drug-delivery and drug-targeting systems. Due to their smallness, they are not recognized by the human body, migrate through cell membranes beneath a critical size and are able to pass the blood–brain barrier. These characteristics are used to develop nanoscale ferries, which transport high potential pharmaceutics precisely to their destination. There are different kinds of nanoparticles which are suitable to be applicable in drug and gene delivery, probing DNA structures, etc., and are categorized as liposomes, polymer nanoparticles (nanospheres and nanocapsules), solid lipid nanoparticles, nanocrystals, polymer therapeutics such as dendrimers and fullerenes (most common as C60 or buckyball, similar in size of hormones and peptide a-helices) and inorganic nanoparticles (e.g. gold and magnetic nanoparticles).

Carbon nanotubes (diameter of 1–20 nm, as shown in Fig. 1.2a) and *inorganic nanowires* exhibit extraordinary mechanical, electric, electronic, thermal and optical properties, offering the electronic industry properties that few materials platforms could ever hope to match. Carbon nanotubes, magnetic iron oxide nanoparticles

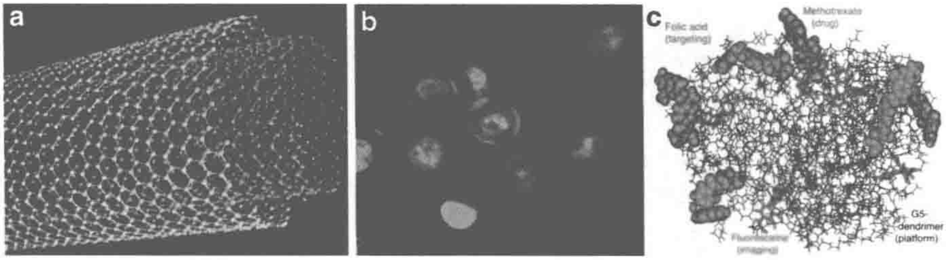

Fig. 1.2 Representative types of nanomaterials and nanoparticles: (**a**) Carbon nanotube, (**b**) human breast cancer cells tagged with quantum dots and (**c**) dendrimer [4]

and gold-coated silica nanoshells can transform electromagnetic energy into heat, causing a temperature increase lethal to cancer cells merely by increasing the magnetic field or by irradiation with an external laser source of near-infrared (NIR) light at the very location where these nanoparticles are bound to or internalized within tumour cells [3]. CNTs can be used as potential drug carriers as well. Pharmaceutical cargos are bound to nanotubes where specific biomolecules that target specific cell types are also attached [5].

Quantum dots (nanometre-sized semiconductor nanocrystals with superior fluorescent properties, as shown in Fig. 1.2b) possess remarkable optical and electronic properties that can be precisely tuned by changing their size and composition, due to their very small size (2–10 nm). Due to their relatively inexpensive and simple synthesis, quantum dots have already entered the market for experimental biomedical imaging applications. Quantum dots can be made to emit light at any wavelength in the visible and infrared ranges and can be inserted almost anywhere, including liquid solution, dyes, etc. These novel nanostructures can play an important role in future biomedical imaging and diagnostics. A hypothetical approach proposes the simultaneous usage of many quantum dots with different physicochemical properties for imaging applications. In particular, this would require a complicated system where a variety of surface ligands with unique specificity for different targets in patient's body are attached to each different quantum dot. So the resulting quantum dot–ligand conjugates would be used as imaging agents for a multiple-target in vivo detection application like the one shown in Fig. 1.3 [3, 4, 6, 7].

Dendrimers (complex almost spherical macromolecules with diameter 1–10 nm, shown in Fig. 1.2c) have improved physical, chemical and biological properties compared to traditional polymers. Some unique properties are related to their globular shape and the presence of internal cavities, offering the possibility as medical nanovehicles. Dendrimers have a tree-like structure where a central nucleus is surrounded by a large number of branches where a variety of molecules, including drugs, can be attached. Less than 5 nm in diameter, dendrimers are small enough to slip through tiny openings in cell membranes and to pass vascular pores and tissues in a more efficient way than bigger polymer particles. The architectural structure of dendrimers can be easily controlled during the synthesis process making them ideal candidates for drug-delivery applications. In experiments reported in Cancer