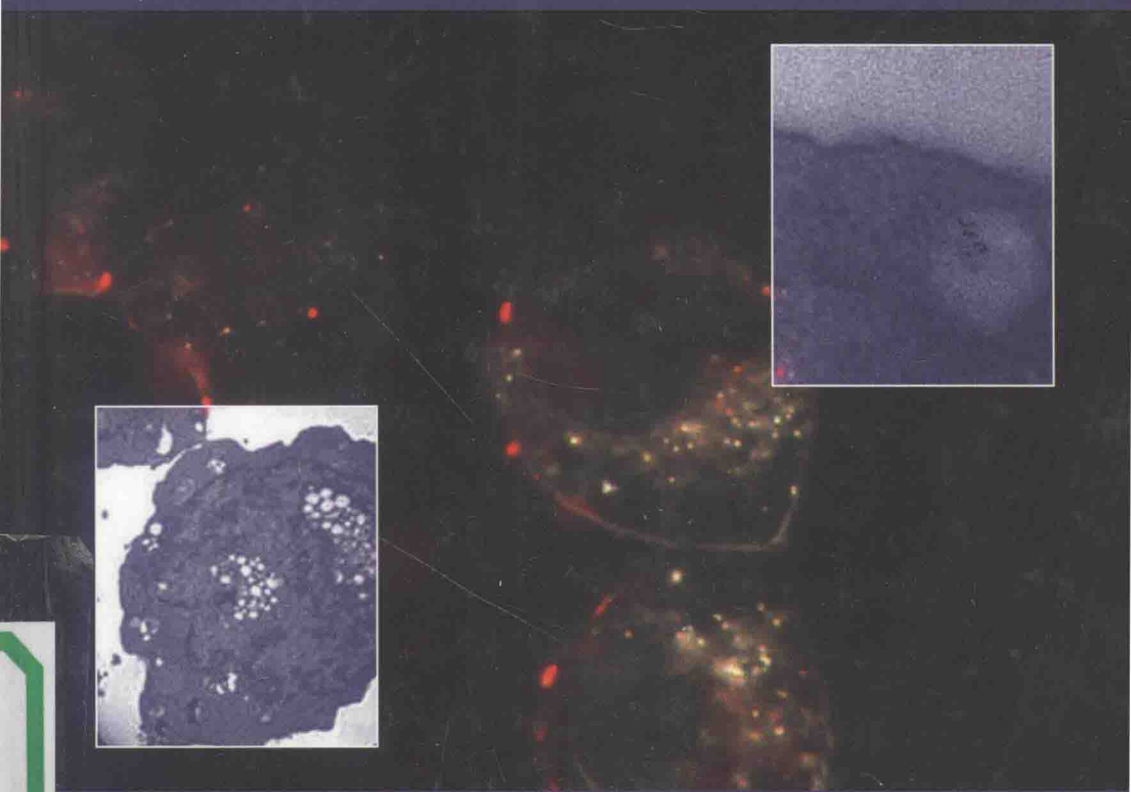
ELSEVIER

Frontiers of Nanoscience
Series Editor: Richard E. Palmer

Volume 5

Nanomedicine



Edited by
Huw Summers

Nanomedicine

Edited by

Huw Summers
Systems and Process Engineering Centre, College of Engineering,
Swansea University, Singleton Park,
Swansea, United Kingdom

ELSEVIER

Amsterdam • Boston • Heidelberg • London • New York • Oxford
Paris • San Diego • San Franciso • Singapore • Sydney • Tokyo

Elsevier
The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, UK
Radarweg 29, PO Box 211, 1000 AE Amsterdam, The Netherlands

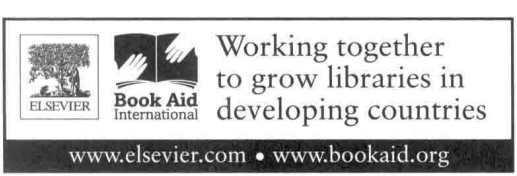
British Library Cataloguing in Publication Data
A catalogue record for this book is available from the British Library

Library of Congress Cataloging-in-Publication Data
A catalog record for this book is available from the Library of Congress

ISSN: 1876-2778
ISBN: 978-0-08-098338-7

Printed and bound in Poland

13 14 15 16 17 11 10 9 8 7 6 5 4 3 2 1



Nanomedicine

FRONTIERS OF NANOSCIENCE

Series Editor: Richard E. Palmer
The Nanoscale Physics Research Laboratory,
The School of Physics and Astronomy,
The University of Birmingham, UK

Vol. 1 **Nanostructured Materials** edited by
Gerhard Wilde

Vol. 2 **Atomic and Molecular Manipulation** edited by
Andrew J. Mayne and Gérald Dujardin

Vol. 3 **Metal Nanoparticles and Nanoalloys** edited by
Roy L. Johnston and J.P. Wilcoxon

Vol. 4 **Nanobiotechnology** edited by
Jesus M. de la Fuente and V. Grazu

Vol. 5 **Nanomedicine** edited by
Huw Summers

Contributors

Numbers in Parentheses indicate the pages on which the author's contributions begin.

Sally Ally (139), Department of Nanomedicine, The Methodist Hospital Research Institute, Houston, TX 77030

Andy Brown (95), Institute for Materials Research, SPEME, University of Leeds, Leeds, United Kingdom

Serena A. Corr (29), School of Chemistry, University of Glasgow, University Avenue, Glasgow, United Kingdom

F.J. Currell (65), Centre for Plasma Physics, School of Mathematics and Physics, Queen's University, Belfast, Northern Ireland, United Kingdom

Biana Godin (139), Department of Nanomedicine, The Methodist Hospital Research Institute, Houston, TX 77030

Javier Gonzalez (139), Department of Nanomedicine, The Methodist Hospital Research Institute, Houston, TX 77030

Nicole Hondow (95), Institute for Materials Research, SPEME, University of Leeds, Leeds, United Kingdom

Fransisca Leonard (139), Department of Nanomedicine, The Methodist Hospital Research Institute, Houston, TX 77030

S.J. McMahon (65), Centre for Cancer Research and Cell Biology, School of Medicine and Dentistry, Queen's University, Belfast, Northern Ireland, United Kingdom

Ismail M. Meraz (139), Department of Nanomedicine, The Methodist Hospital Research Institute, Houston, TX 77030

Paul Rees (123), Broad Institute of MIT and Harvard, Cambridge, Massachusetts, USA; Centre for Nanohealth, College of Engineering, Swansea University, Swansea, United Kingdom, and Department of Nanomedicine, The Methodist Hospital Research Institute, Houston, Texas, USA

Victor Segura-Ibarra (139), Department of Nanomedicine, The Methodist Hospital Research Institute, Houston, TX 77030

Rita E. Serda (139), Department of Nanomedicine, The Methodist Hospital Research Institute, Houston, TX 77030

Huw Summers (1), Systems and Process Engineering Centre, College of Engineering, Swansea University, Singleton Park, Swansea, United Kingdom

Marc J. Williams (29), School of Physical Sciences, University of Kent, Canterbury, United Kingdom

Preface

Nanomedicine may be defined as the application of nanotechnology to detect and to treat disease. As in many other areas of nanoscience, the control of materials at the nanometre scale allows radically new approaches; these promise to revolutionise medical practise. The fundamental aspect of nanomedicine comes from the ability to engineer structures on the molecular scale and so intervene within cells to alter the biochemical interactions which are the genesis of disease in the body. While the universal property of size-controlled characteristics in nanomaterials will be well known to physical scientists and engineers, its application within the human body brings us to unfamiliar territory, in which technology must be viewed as dynamic, ever changing, as it is subject to the influence of the biological systems in which it is placed. The application of nanotechnology within biological cells can fundamentally alter them, but in turn the cell alters the physiochemical properties of the nanomaterial. Thus the as-engineered nanoparticle is just a starting point and the characteristics of nanomaterials within nanomedicine must be constantly reassessed if their diagnostic and therapeutic value is to be fully realised. To highlight this point, this volume begins with an overview of the basic principles of nanomedicine in the context of the most profound of reactive biological systems—the immune response. This constitutes an organised attack by the whole organism on the nanoparticulate, foreign bodies. Our bodies have evolved over millennia to deal with 'natural', virus nanoparticulates, and the details of virus–white blood cell interactions are presented as an illustration of both the power of nanomedicine and the challenges it must overcome.

Detailed expositions on the use of magnetic and metallic nanoparticles for theranostics, simultaneous detection and treatment of disease, are presented in Chapters 2 and 3. Magnetic particles can be used to enhance the contrast in magnetic resonance imaging techniques, to kill targeted cells through localised heating or to deliver drugs to specified areas of the body under the guidance of magnetic fields. In a similar manner, gold particles can enhance X-ray imaging and provide localised amplification of therapeutic effect in radiation treatments. These examples vividly portray the exciting potential of nanomedicine; here science and technology are locating diseased cells, clearly marking them, for the clinician to see, and helping to selectively kill or reprogram these rogue cells.

In any area of medical science, it is crucially important to know accurately the level of dose being administered and this is especially important in nanomedicine where the nanotherapeutic is delivered directly inside cells.

Chapters 4 and 5 cover various aspects of the question of dose assessment and the understanding of particle–cell interactions. In this endeavour, nanotechnology provides the analytical instrument as well as the medical intervention. Nanoscale imaging and quantitative nano-metrology are required, and techniques such as electron microscopy, and quantum dot based, fluorescence imaging are important tools. These chapters on nanoparticle dose reinforce the need to monitor particle properties in the biological medium and reiterate the subtle complexities of particle uptake, distribution and alteration within cells.

The volume ends with a look at nanomedicine in the context of the diseased state as it is manifested across the whole organism. Here a wider look at the impact of nanotechnology, beyond the single cell, is employed. The question of how nanostructures can help in targeting and treating human disease in its complex reality of multiple cell types within varied and evolving biological niches is addressed. This is a look at nanomedicine from the viewpoint of medical science, providing a closing chapter that highlights, for physical scientists and engineers, the viewpoint of the end-user of our technology.

Huw Summers

Contents

Chapter 1

Nanomedicine—Biological Warfare at the Cellular Level

Huw Summers

Systems and Process Engineering Centre, College of Engineering, Swansea University, Singleton Park, Swansea, United Kingdom

1 INTRODUCTION

Every day of our lives, our bodies are locked in a battle with a myriad of nano- and microscale pathogens seeking to subvert our cells. On one side of this battle, viruses, bacteria and other micro-organisms are the causes of widespread and often deadly diseases such as malaria, cholera, HIV/AIDS and tuberculosis. In response to these threats our immune system constantly monitors for foreign invaders, marking 'non-self' entities with antibodies and then destroying them through an army of specialised cells and chemical agents.[1] This is the battleground on which Nanomedicine is pursued; nanoparticles, when introduced to the body, will be seen as foreign bodies and are subjected to the full armoury of the body's defence system. They will be labelled with antibody molecules and then targeted by phagocytic white blood cells which will engulf them and clear them from the blood stream into organs such as the spleen, liver and kidneys. Thus, the challenge for nanotechnologists is to use stealth to avoid these defences so that nanotherapeutics remain in the blood stream for long enough to reach their destination, enter selected cells and deliver drugs to their target. This involves crossing biological boundaries such as the lipid membrane that encapsulates the cell or the nuclear envelope around its DNA. I have used this language of 'conflict' to emphasise that the interaction of nanoparticles with the body's organs and cells is an active, adaptive process in which the particles are subject to chemical attack and physical removal from the system. In short, nanomedicine may be viewed as a war between our technology and our bodies, carried out at the molecular level. Nanoparticles are our weapons of attack with an ability to penetrate the cell's defensive barriers and directly modify the networks and pathways of molecular interaction which are the primary drivers of disease. In response, the complex and intricate immune system is the body's first line of defence, stopping nanotherapeutics from reaching their intended destination. Even if

Frontiers of Nanoscience, Vol. 5. http://dx.doi.org/10.1016/B978-0-08-098338-7.00001-7

the cell is breached, there are intra-cellular defences such as the endosome–lysosome system, which can encapsulate particles and lock them away from the rest of the cell within membrane-bound vesicles. One of the biggest challenges in nanomedicine is to develop particles that can 'break out' of these membrane cages and so deliver drugs to areas where they can alter the control machinery of the cell, for example, the nucleus.

The dynamic nature of this battle calls for a constant evolution in strategy. This is evident in the rapidly expanding research base of nanomedicine: particles with novel geometries and chemical composition are constantly being produced through ever-evolving synthesis routes in multi-layer, multifunctional forms that can provide controlled action of a bespoke nature in predefined cells. This innovation is essential as nanomedicines must contend with the evolutionary adaptation of the innate immune system, selected through biological fitness to deal effectively with nanoscale invaders and the rapid responses of the adaptive immune system which can identify specific pathogens mount an attack within hours. Figure 1.1 provides a schematic overview of this battle, detailing the key steps of particle–cell interactions and highlighting the tension between the drive to affect therapeutic outcomes using nanoparticles and the immune response of the host which tends to negate this.

Nanomedicine is a very broad research field encompassing diverse application areas such as diagnostics, therapeutics, biomedical devices and medical imaging.[2–6] In this work, I focus solely on the use of nanotechnology to engineer therapeutics agents, that is, nanomedicines: nanoparticulates that provide drug delivery systems or that directly act as therapeutic agents.

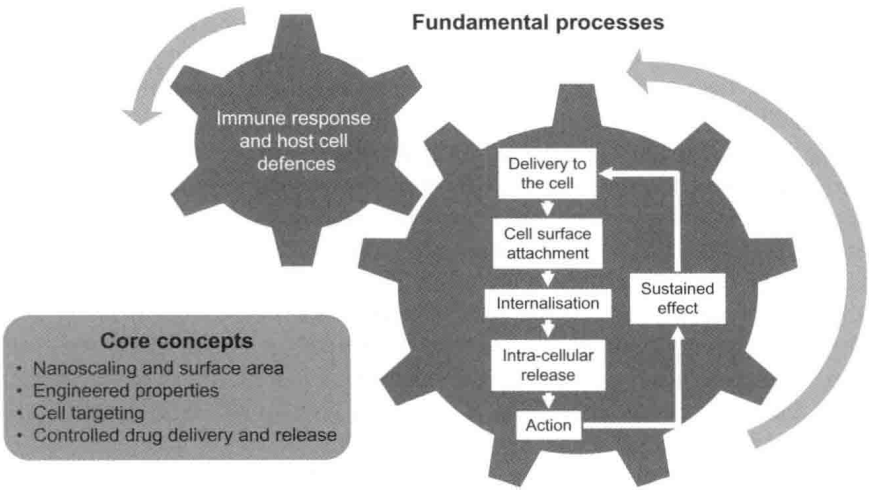


FIGURE 1.1 A schematic of the fundamental processes and core concepts in nanomedicine. (For colour version of this figure, the reader is referred to the online version of this chapter.)

This book is aimed at physical scientists and engineers and so the foray into medicine takes us into unfamiliar territory. I have therefore chosen the conceptual model of bio-warfare to give the reader an understanding of the landscape of nanomedicine—its general outline, common themes and points of interaction and control. A detailed account of the molecular biology, physiology and pharmacology at the heart of the subject is clearly beyond the scope of this text, but we can understand how the whole picture fits together without resolving the detail.

This concept of warfare highlights key themes to be found in nanomedicine which are likely to be unfamiliar to the physical scientist or engineer working on nanotechnology:

1. *Interaction*: Cells are not a passive environment into which nanoparticles are introduced, they are active participants in any treatment or experiment and are able to influence their interactions with nanoparticles and adapt their response.
2. *Alteration*: Bio-activity can, and usually does, change the physiochemical properties of the nanoparticle, either through coating of the particle surface with bio-molecules or through chemical reaction with the material of the particle shell and core. This requires a different point of view to that usually employed in nanotechnology, the design and synthesis of engineered particles to produce certain characteristics are only the first phase of a life cycle that will see the particle's properties radically altered upon entry into a biological system.
3. *Adaptation*: Change is essential when dealing with dynamic biological systems able to respond and adapt. Successfully delivering a nanotherapeutic to a cell and effecting a favourable outcome require the control of a series of spatial and temporal factors; for example, multifunctional particles have to locate and attach to the cell surface, then enter the cell and at some later time release a drug cargo, often in response to an activating trigger such as pH level. This dynamic of drug delivery must also take account of the natural cycles of cell growth and proliferation.

The warfare model is best exemplified by the ultimate nanoscale agent—the virus particle (known as a *virion*), an evolved, bio-nanoparticle. These are similar to engineered nanoparticles in scale, geometry and structure, and their biology offers us a guide through which we can understand nanoparticle–cell interactions from a familiar vantage point. If anyone doubts the potential of nanomedicines, they should think of the efficiency with which influenza virions enter cells and wreak system wide havoc in our body! The example of the virus particle reminds us that while nanomedicine is relatively new, human exposure to nanoparticles is not. Our bodies have been fighting viruses for millennia, evolving multiple defence strategies to minimise their effect. It is worth pausing to reflect on this: the body is well prepared to evade nanomedicines and a decade or so of intense research activity on engineered particles

cannot match the 300 million years of evolution and the continuing adaptive ability that has led to perfected viruses that can produce new strains in a time-frame of a few years.

2 NANOPARTICLES WITHIN A BIOLOGICAL ENVIRONMENT

2.1 How Big is Biology?

While readers of this series are very familiar with the nanometre scale and the conceptualisation of a 'billionth of a metre', they are perhaps less able to relate this to the biological world.[7] The fundamental unit in living systems is the cell and this is the organisational unit from which complex organisms are constituted, housing the key machinery of protein production and the essential gene code from which all life ensues. An electron micrograph of a human cell section is shown in Figure 1.2 to provide a guide to the scale of various cellular structures. Cells vary hugely in size and shape but as a general class can be said to be microscale objects; the human fibroblast cell depicted in Figure 1.2 grows as a flattened film of thickness 1–2 μm and a lateral dimension of ~15 μm. Cells are defined by their membrane; this is a bilayer structure composed of phospholipid molecules, with hydrophobic tail and hydrophilic head groups, which self-assemble into a double sheet of molecules that is 2–3 nm in thickness.[8,9] Within the cell, the largest sub-cellular structure is the nucleus, which in mammalian cells is ~6 μm in diameter,[1] this houses the cellular DNA in the form of chromosomes.

The DNA molecule itself is truly nanoscale, consisting of a double helix of nucleotide base units on a backbone of alternating sugar and phosphate

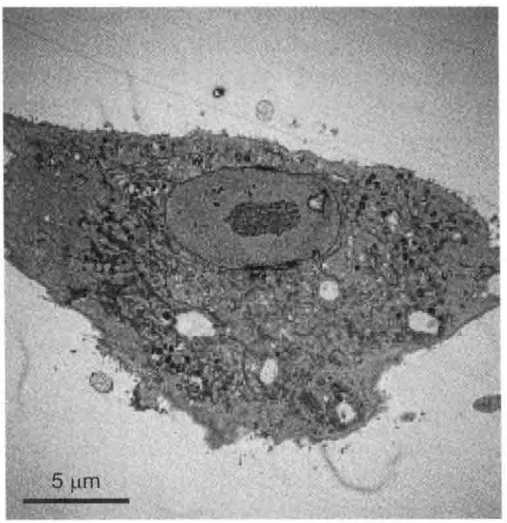


FIGURE 1.2 An electron micrograph of an U2-OS, Osteosarcoma cell section.