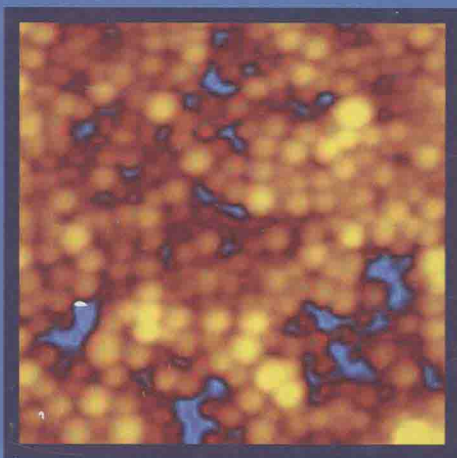
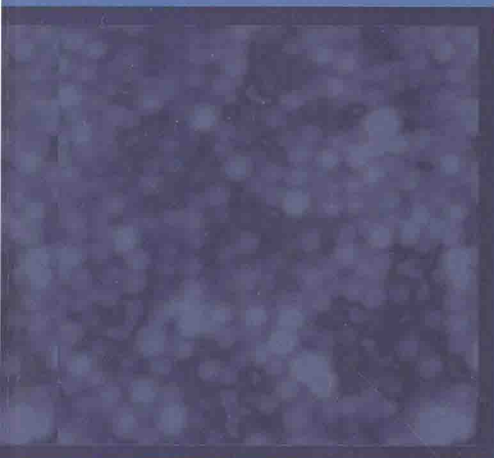


Horizons in Clinical Nanomedicine



edited by
Varvara Karagkiozaki
Stergios Logothetidis

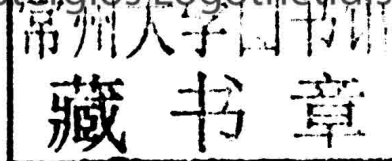


Horizons in Clinical Nanomedicine

edited by

Varvara Karagkiozaki

Stergios Logothetidis



Published by

Pan Stanford Publishing Pte. Ltd.
Penthouse Level, Suntec Tower 3
8 Temasek Boulevard
Singapore 038988

Email: editorial@panstanford.com

Web: www.panstanford.com

British Library Cataloguing-in-Publication Data

A catalogue record for this book is available from the British Library.

Horizons in Clinical Nanomedicine

Copyright © 2015 by Pan Stanford Publishing Pte. Ltd.

All rights reserved. This book, or parts thereof, may not be reproduced in any form or by any means, electronic or mechanical, including photocopying, recording or any information storage and retrieval system now known or to be invented, without written permission from the publisher.

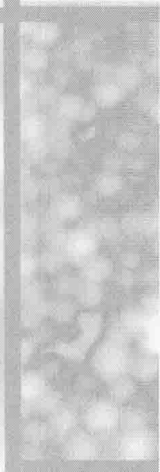
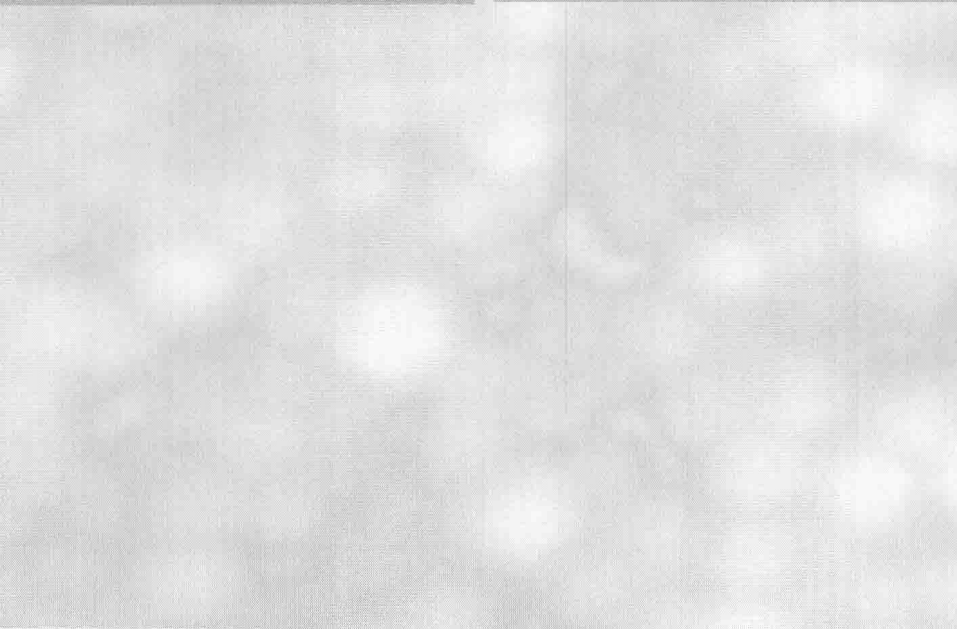
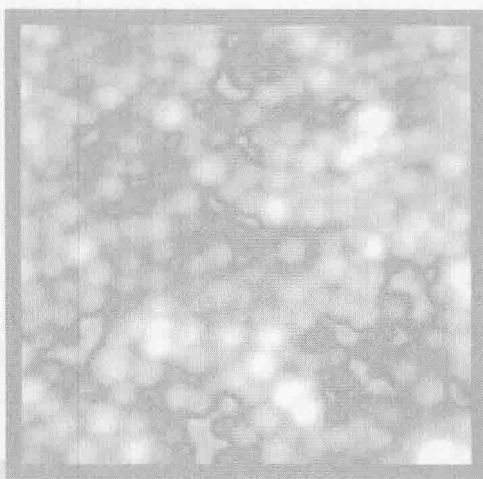
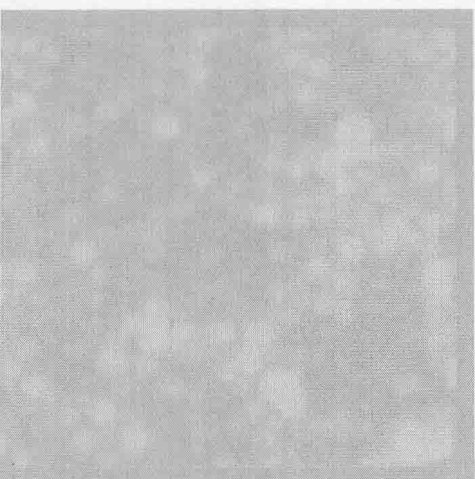
For photocopying of material in this volume, please pay a copying fee through the Copyright Clearance Center, Inc., 222 Rosewood Drive, Danvers, MA 01923, USA. In this case permission to photocopy is not required from the publisher.

ISBN 978-981-4411-56-1 (Hardcover)

ISBN 978-981-4411-57-8 (eBook)

Printed in the USA

Horizons in Clinical Nanomedicine



Preface

Nanomedicine, a flourishing field of medical research, is expected to provide modern medicine with innovative solutions to the unmet and unsolved clinical needs. Nanostructured materials have the potential to revolutionize healthcare, due to their novel intrinsic physicochemical properties which can be exploited towards cutting-edge developments in the fields of diagnosing, treating, and preventing diseases, injuries, or genetic disorders. Thus, clinical nanomedicine holds great promise as a future powerful tool of medicine that improves human health.

This book presents a broad overview on nanomedicine tools, materials, and processes to be applied to different medical disciplines. It presents the broad spectrum of nanomedicines for the early, accurate diagnosis and effective treatment of human diseases. Taking into account the pillars of *in vitro* and *in vivo* nanodiagnostics, regenerative medicine, and nanopharmaceuticals, it deals with the unsolved medical problems in cardiovascular disease, AIDS, cancer, blood diseases, congenital defects, dermatology, dentistry, and orthopaedics, with a focus on personalized medicine. It addresses nanosafety and nanotoxicity issues to highlight the significance of nanomedicine applied into clinical practice for the benefit of the patient. The book will appeal to researchers, medical doctors, and graduate students who want to get in-depth knowledge of nanomedicine utilities for clinical applications.

Contents

<i>Preface</i>	xiii
1. Introduction in Clinical Nanomedicine	1
<i>Stergios Logothetidis</i>	
1.1 Introduction	2
1.2 Nanomedicine and Diversity of Nanocarriers	5
1.3 Nanomedicine in Regenerative Medicine	9
1.4 Nanomedicine in the Early Diagnosis of Diseases	12
1.4.1 In vitro Diagnostics	13
1.4.2 In vivo Diagnostics	18
1.5 Targeted Drug Delivery	21
1.5.1 Nanocarrier-Based Drug Delivery Systems	21
1.5.2 Clinical Applications for Nanocarrier-Based Drug Delivery	23
1.5.3 Drug Targeting Approaches	26
1.6 Nanotoxicology and Safety Aspects	28
1.7 Conclusions	29
2. Nanomedicine Combats Atherosclerosis	39
<i>Varvara Karagkiozaki</i>	
2.1 Introduction	39
2.2 Understanding of Atherosclerosis	41
2.3 Nanomedicine for Accurate Diagnosis of Atherosclerosis	44
2.4 Nanomedicine in Atherosclerosis Treatment	51
2.4.1 Therapeutic Nanoparticles	51
2.4.2 Nanomedicine for Stents	53
2.5 Conclusions and Future Perspectives	56
3. Nanomedicine Advancements in Cancer Diagnosis and Treatment	67
<i>Eric Michael Bratsolias Brown</i>	
3.1 Introduction	67

3.2	Unique Properties of Gold, Iron oxide, and Titanium Dioxide Nanoparticles That Benefit Cancer Applications	69
3.3	Use of Gold, Iron Oxide, and Titanium Dioxide Nanoparticles in Cancer Diagnosis	71
3.4	Use of Gold, Iron Oxide, and Titanium Dioxide Nanoparticles in Cancer Therapy	75
3.5	Development of Gold, Iron Oxide, and Titanium Dioxide Nanoparticles for Cancer Theranostics	78
3.6	Conclusion	79
4.	Nanomedicine and Blood Diseases	93
	<i>Emmanouil Nikolousis</i>	
4.1	Introduction: Haematological Malignancy Outcomes	93
4.1.1	Acute Myeloid Leukaemia Outcomes	94
4.2	Major Achievements in Haematology over the Last Decade	97
4.2.1	Targeted Therapy for Chronic Myeloid Leukaemia	97
4.2.2	Immunotherapy for Non-Hodgkin Lymphoma	98
4.3	Nanotechnology and Its Use in Haematology: Background	99
4.3.1	Passive Targeting	101
4.3.2	Active Targeting	101
4.3.3	Destruction from Within	101
4.4	Nanotechnology and Diagnosis for Haematological Diseases	102
4.5	Nanotechnology in Specific Haematological Cancers	103
4.5.1	Mantle Cell Lymphoma	103
4.5.2	CNS Lymphomas	105
4.5.3	Acute Leukaemias	106
4.5.4	Chronic Myeloid Leukaemia	107
4.5.5	Multiple Myeloma	108
4.6	Major Challenges Facing the Use of Nanotechnology in Haematology	109
4.7	Conclusion	110

5. Nanomedicine and Orthopaedics	115
<i>Fares E. Sayegh</i>	
5.1 Introduction	115
5.2 The Role of Nanomedicine in Early Screening of Orthopaedic Diseases	117
5.3 Nano Biologically Active materials and Conservative Treatment of Early OA	117
5.4 Nanotechnology and Nanobiomaterials in the Treatment of Advanced OA	118
5.5 Tissue Engineering in Orthopaedics	121
5.6 Conclusion	123
6. Nanopharmaceutics: Structural Design of Cationic Gemini Surfactant–Phospholipid–DNA Nanoparticles for Gene Delivery	129
<i>Marianna Foldvari</i>	
6.1 Introduction	130
6.2 Gemini Nanoparticles	133
6.3 Nanoparticle Structure Analysis	135
6.4 Nanoparticle Structural Responsiveness and Transfection Efficiency	136
6.5 Conclusions	138
7. Nanomedicine and Embryology: Causative Embryotoxic Agents Which Can Pass the Placenta Barrier and Induce Birth Defects	147
<i>Elpida-Niki Emmanouil-Nikoloussi</i>	
7.1 Introduction	147
7.2 Drugs, Environmental Pollution and Embryotoxicity	150
7.3 Drugs, Nanoparticles and Embryology	160
7.3.1 Causative Embryotoxic Agents Inducing Cellular Apoptosis and Creating Birth Defects	162
7.3.2 Embryonic Development and Nanomolecules	162
7.3.3 Mechanics and Nanomolecules during Development	163

7.3.4	Nanoparticles as a Study Tool in Developmental Processes and Reproductive Toxicology	164
7.4	Placenta Permeability and Nanoparticles	166
7.5	Conclusions	167
8.	Nanomedicine and HIV/AIDS	175
	<i>Enikő R. Tőke and Julianna Lisziewicz</i>	
8.1	Introduction	175
8.2	Nanomedicine in Antiretroviral Drug Development	177
8.3	Nanomedicine in Vaccine Development	179
8.4	DermaVir Clinical Nanomedicine Product Candidate for HIV Immunotherapy	182
8.5	Conclusion	188
9.	Nanoscaffolds and Other Nano-Architectures for Tissue Engineering-Related Applications	195
	<i>Paraskevi Kavatzikidou and Stergios Logothetidis</i>	
9.1	Introduction	195
9.2	Nano-Architectures and Nanoscaffolds	196
9.2.1	Materials	196
9.2.1.1	Natural materials	197
9.2.1.2	Synthetic materials	197
9.2.1.3	Semi-synthetic materials	198
9.2.2	Fabrication Methods	199
9.2.2.1	Electrospinning	199
9.2.2.2	Self-assembly	200
9.2.2.3	Phase separation	201
9.2.3	Different Architectures and Their Properties	201
9.3	Tissue Engineering	202
9.3.1	Introduction	202
9.3.2	Material Requirements	203
9.3.3	Fabrication Methods	203
9.4	Bone and Cartilage Engineering Applications	206
9.4.1	Bone Biology	206
9.4.2	Bone-Related Clinical Problems	207
9.4.3	Bone-Related Applications	208

9.4.4	Nanomaterials for Cartilage Applications	210
9.5	Cardiac Engineering Applications	211
9.6	Nerve Engineering Applications	212
9.7	Correlation of Cell–Material Interactions at the Nanoscale	215
9.8	Conclusions	218
10.	Biocompatible 2D and 3D Polymeric Scaffolds for Medical Devices	229
	<i>Masaru Tanaka</i>	
10.1	Introduction: An Explanation of the Design and Research on Polymeric Biomaterials	230
10.2	Biocompatible Polymers	230
10.3	Protein Adsorption on Polymer Surfaces	232
10.4	Water Structure and Dynamics of Polymer	234
10.5	3D Polymeric Scaffolds for Tissue Engineering	237
10.6	Methods of 3D Scaffold Fabrication	238
	10.6.1 Top-Down Fabrication	238
	10.6.2 Bottom-Up Fabrication	238
10.7	Control of Cell Adhesion and Functions	244
10.8	Conclusions and Perspectives	246
11.	Regenerative Dentistry: Stem Cells meet Nanotechnology	255
	<i>Lucía Jiménez-Rojo, Zoraide Granchi, Anna Woloszyk, Anna Filatova, Pierfrancesco Pagella, and Thimios A. Mitsiadis</i>	
11.1	Introduction	255
11.2	Dental Stem Cells	256
	11.2.1 Dental Mesenchymal Stem Cells	257
	11.2.1.1 Dental pulp stem cells	257
	11.2.1.2 Stem cells from human exfoliated deciduous teeth	258
	11.2.1.3 Stem cells from the apical part of the papilla	259
	11.2.1.4 Periodontal ligament stem cells	260
	11.2.1.5 Stem cells from the dental follicle	260

11.2.2	Dental Epithelial Stem Cells	261
11.2.2.1	Epithelial stem cells in rodent incisors	261
11.2.2.2	Epithelial stem cells in human teeth	263
11.3	Regenerative Dentistry	264
11.3.1	Approaches for Tooth Regeneration	265
11.3.1.1	Regeneration of the pulp /dentin complex	266
11.3.1.2	Regeneration of periodontal tissues	267
11.3.1.3	Regeneration of enamel	268
11.3.1.4	Regeneration of an entire tooth	268
11.3.1.5	Challenges of dental tissue regeneration	270
11.4	Stem Cells Meet Nanotechnology	271
11.4.1	Follow-Up of Stem Cells after Transplantation	272
11.4.1.1	Magnetic nanoparticles	272
11.4.1.2	Quantum dots	273
11.4.2	Gene, Protein and Drug Intracellular Delivery	273
11.4.3	Nanobiomimetics	274
11.4.3.1	Nanotechnology for the design of artificial stem cell niches	274
11.4.3.2	Design of nanofiber scaffolds	275
11.5	Conclusions	276
12.	Toxicity and Genotoxicity of Metal and Metal Oxide Nanomaterials: A General Introduction	289
	<i>Mercedes Rey, David Sanz, and Sergio E. Moya</i>	
12.1	Introduction	289
12.2	Effect of Different Metal and Metal Oxide Nanoparticles on the Immune Response	292
12.2.1	Titanium Dioxide Nanoparticles	292
12.2.2	Zinc Oxide Nanoparticles	292
12.2.3	Iron Oxide Nanoparticles	294
12.2.4	Cerium Oxide Nanoparticles	297

12.2.5	Gold Nanoparticles	297
12.2.6	Silver Nanoparticles	299
12.2.7	Silica Nanoparticles	300
12.2.8	Copper Nanoparticles	301
12.3	Metallic Nanoparticles and Their Interactions with Plasma Proteins	302
12.4	Intracellular Signalling Pathways Activated by Metallic Nanoparticles	303
12.5	Genotoxic Studies on NMs	304
12.5.1	ZnO Nanoparticles	304
12.5.2	Aluminium Oxide	305
12.5.3	TiO ₂ Nanoparticles	305
12.5.4	CeO ₂ Nanoparticles	306
12.5.5	Gold Nanoparticles	307
12.5.6	Silver Nanoparticles	308
12.5.7	Platinum Nanoparticles	309
12.5.8	Fe ₃ O ₄ Nanoparticles	309
12.6	Conclusions	309
13.	Analogies in the Adverse Immune Effects of Wear Particles, Environmental Particles, and Medicinal Nanoparticles	317
	<i>Eleonore Fröhlich</i>	
13.1	Introduction	317
13.2	Orthopaedic Implants	318
13.2.1	Common Joint Replacements	318
13.2.1.1	Hip replacement implants	320
13.2.1.2	Knee replacement implants	320
13.2.1.3	Shoulder	321
13.2.1.4	Elbow	321
13.2.2	Failure of Implants	321
13.2.2.1	Infection	321
13.2.2.2	Aseptic loosening	322
13.2.2.3	Generation of particles	322
13.2.2.4	Unspecific and specific immune response	322
13.3	Environmental Particles	326
13.3.1	Immune Effects of Environmental Particles	328
13.3.1.1	Diesel exhaust particles	328

	13.3.1.2	Carbon black	330
	13.3.1.3	Role of contaminants in the immune reaction to diesel exhaust particles	331
13.4		Medical Nanoparticles	332
	13.4.1	Use of Non-Biodegradable Nanoparticles in Medicine	332
	13.4.2	Immunotoxicity and Effects of Medical Nanoparticles on the Immune System	332
	13.4.2.1	Iron oxide nanoparticles	333
	13.4.2.2	Gold nanoparticles	333
	13.4.2.3	Silver nanoparticles	333
	13.4.2.4	Silica nanoparticles	334
	13.4.2.5	Carbon nanotubes	334
	13.4.2.6	Size-dependency of the immune effects	335
	13.4.2.7	Comparison of immune effects of different particles	335
13.5		Conclusions	338
		<i>Index</i>	349

Chapter 1

Introduction in Clinical Nanomedicine

Stergios Logothetidis

*Lab for Thin Films—Nanosystems and Nanometrology,
Department of Physics, Aristotle University of Thessaloniki,
54124 Thessaloniki, Greece
logot@auth.gr*

Nanotechnology represents the possibility of revolutionising many aspects of our lives. Nanomedicine, the application of nanotechnology to health, is one of the most promising fields of biomedical research, building up a novel research culture by encompassing the principles of traditional disciplinary boundaries (i.e., physics, chemistry, biology and engineering). Nanomedicine has the potential to give intelligent solutions to many of the current medical problems, by opening the door to a new generation of advanced drug delivery systems, improved diagnostic systems (in vitro and in vivo) and novel methods and materials for regenerative medicine. There are currently two families of therapeutic nanocarriers (i.e., liposomes and albumin nanoparticles) that have been approved and used in clinical settings, providing clinical benefit. Moreover, several nanocarriers are in clinical trials and even more are in pre-clinical

Horizons in Clinical Nanomedicine

Edited by Varvara Karagkiozaki and Stergios Logothetidis

Copyright © 2015 Pan Stanford Publishing Pte. Ltd.

ISBN 978-981-4411-56-1 (Hardcover), 978-981-4411-57-8 (eBook)

www.panstanford.com

phases. Despite the cutting-edge developments in nanomedicine, the process of converting basic research to viable products is expected to be long and ambitious. A crucial factor that should also be taken into consideration is the toxic effects of the novel therapeutical products in human health. Thus, a massive effort is required to translate laboratory innovation to the clinic and begin to change the landscape of medicine.

1.1 Introduction

Richard Feynman in 1959¹ was the first one to claim that ‘there is plenty of room at the bottom’, and since then, a booming interest in studying the nanoscale has emerged. The nano prefix comes from the Greek word ‘Nano’ meaning dwarf, with 1 nanometre (nm) being equal to one billionth of a metre (10^{-9} m), or 10 water molecules, or about the width of six carbon atoms. Atoms are smaller than 1 nm, whereas many molecules, including proteins, can range in size from 1 nm to several hundreds, as shown in Fig. 1.1.² Studying at such scales is of great importance, as the properties of matter differ significantly, especially due to quantum effects and the large surface-to-volume atom ratio. As a result, new findings arise, contributing to a better understanding of science.

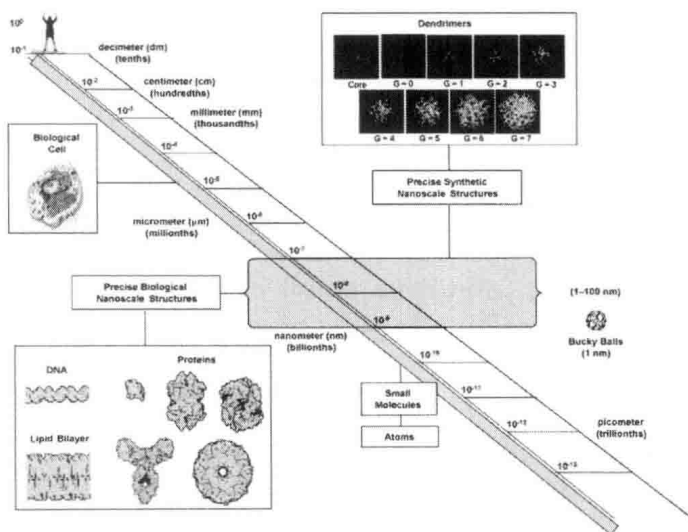


Figure 1.1 Nanoworld and Macroworld: the scale of natural objects.³