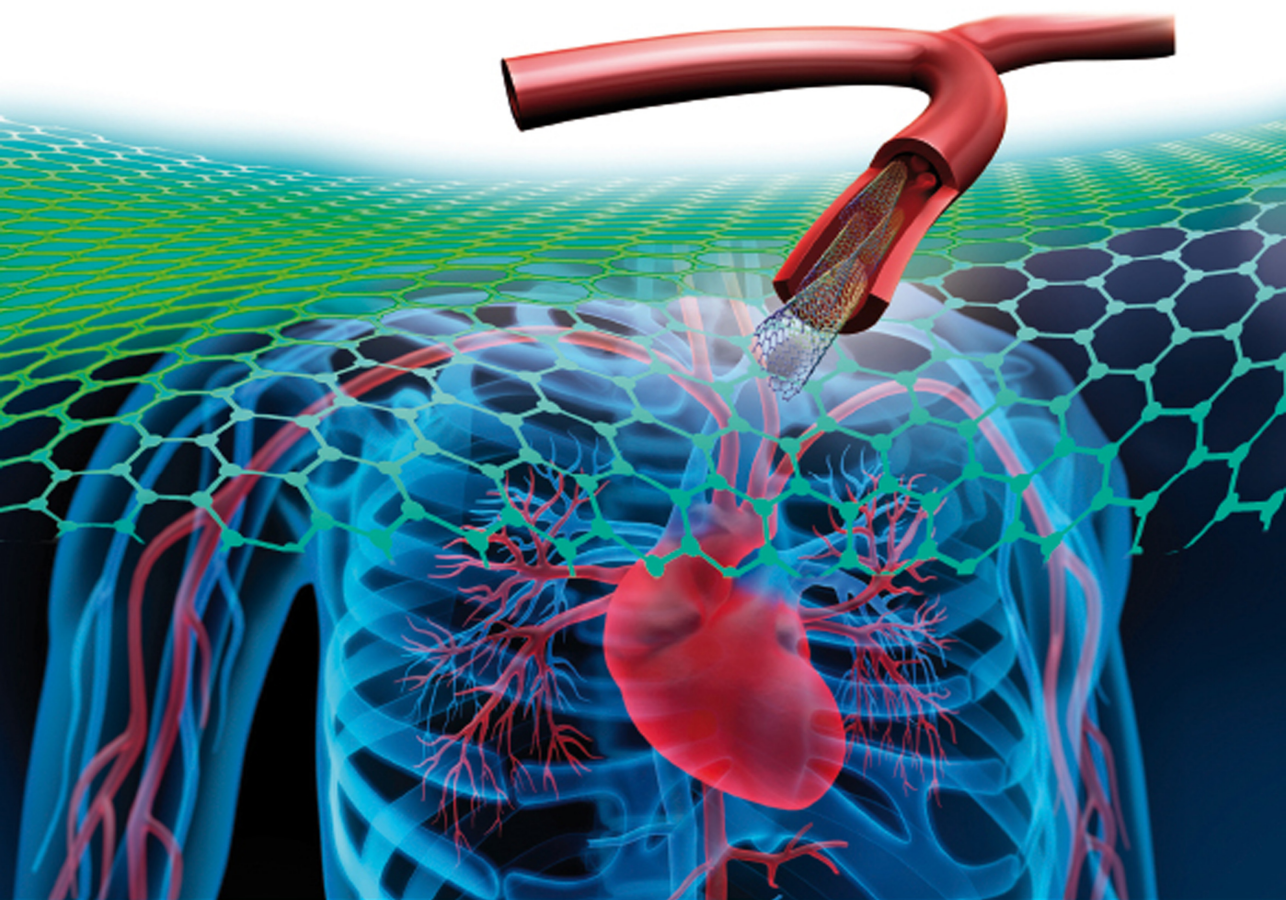


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Volume Editors

Prof. Bert Müller

University of Basel
Department of Biomedical Engineering
Biomaterials Science Center
Gewerbstrasse 14
4123 Allschwil, Switzerland

Prof. Dr. Dr. h.c. Marcel H. Van de Voorde

Member of the Science Council
of the French Senate and National
Assembly, Paris
Rue du Rhodania, 5
BRISTOL A, Appartement 31
3963 Crans-Montana
Switzerland

Series Editor

Prof. Dr. Dr. h.c. Marcel H. Van de Voorde

Member of the Science Council
of the French Senate and National
Assembly, Paris
Rue du Rhodania, 5
BRISTOL A, Appartement 31
3963 Crans-Montana
Switzerland

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*Thanks to my wife for her patience with me spending
many hours working on the book series through
the nights and over weekends.
The assistance of my son Marc Philip related to the complex
and large computer files with many sophisticated scientific
figures is also greatly appreciated.*

Marcel Van de Voorde

Series Editor Preface

Since years, nanoscience and nanotechnology have become particularly important technology areas worldwide. As a result, there are many universities that offer courses as well as degrees in nanotechnology. Many governments including European institutions and research agencies have vast nanotechnology programmes and many companies file nanotechnology-related patents to protect their innovations. In short, nanoscience is a hot topic!

Nanoscience started in the physics field with electronics as a forerunner, quickly followed by the chemical and pharmacy industries. Today, nanotechnology finds interests in all branches of research and industry worldwide. In addition, governments and consumers are also keen to follow the developments, particularly from a safety and security point of view.

This books series fills the gap between books that are available on various specific topics and the encyclopedias on nanoscience. This well-selected series of books consists of volumes that are all edited by experts in the field from all over the world and assemble top-class contributions. The topical scope of the book is broad, ranging from nanoelectronics and nanocatalysis to nanometrology. Common to all the books in the series is that they represent top-notch research and are highly application-oriented, innovative, and relevant for industry.

The titles of the volumes in the series are as follows:

Human-related nanoscience and nanotechnology

- *Nanoscience and Nanotechnology for Human Health*
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Nanoscience and nanotechnology in information and communication

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Nanoscience and nanotechnology in industry

- Nanotechnology for Energy Sustainability
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- Nanotechnology in Catalysis: Applications in the Chemical Industry, Energy Development, and Environmental Protection

The book series appeals to a wide range of readers with backgrounds in physics, chemistry, biology, and medicine, from students at universities to scientists at institutes, in industrial companies and government agencies and ministries.

Ever since nanoscience was introduced many years ago, it has greatly changed our lives – and will continue to do so!

March 2016

Marcel Van de Voorde

About the Series Editor



Marcel Van de Voorde, Prof. Dr. ir. Ing. Dr. h.c., has 40 years' experience in European Research Organisations, including CERN-Geneva and the European Commission, with 10 years at the Max Planck Institute for Metals Research, Stuttgart. For many years, he was involved in research and research strategies, policy, and management, especially in European research institutions.

He has been a member of many Research Councils and Governing Boards of research institutions across Europe, the United States, and Japan. In addition to his Professorship at the University of Technology in Delft, the Netherlands, he holds multiple visiting professorships in Europe and worldwide. He holds a doctor honoris causa and various honorary professorships.

He is a senator of the European Academy for Sciences and Arts, Salzburg, and Fellow of the World Academy for Sciences. He is a member of the Science Council of the French Senate/National Assembly in Paris. He has also provided executive advisory services to presidents, ministers of science policy, rectors of Universities, and CEOs of technology institutions, for example, to the president and CEO of IMEC, Technology Centre in Leuven, Belgium. He is also a Fellow of various scientific societies. He has been honored by the Belgian King and European authorities, for example, he received an award for European merits in Luxemburg given by the former President of the European Commission. He is author of multiple scientific and technical publications and has coedited multiple books, especially in the field of nanoscience and nanotechnology.

Contents

Nanomedicine: Present Accomplishments and Far-Reaching Promises *XXI*

Part One Introduction to Nanoscience in Medicine of the Twenty-First Century *1*

- 1 Challenges and Opportunities of Nanotechnology for Human Health** *3*
Bert Müller
 References *6*
- 2 Nanoscience and Nanotechnology and the Armory for the Twenty-First Century Health Care** *9*
Marcel Van de Voorde and Pankaj Vadgama
- 2.1 Conceptual Dream *9*
 2.2 A Real World Encounter *9*
 2.3 Mapping the Microcosm of Disease *10*
 2.4 Delivery at the Clinical “Coal Face” *10*
 2.5 A High Precision Aim for Disease Targets *10*
 2.6 A Materials Revolution for Clinical Care *11*
 2.7 Robotics for Microrepair and Healing *12*
 2.8 A Dialog with Cells *12*
 2.9 Stealth Materials for a More Potent Delivery *13*
 2.10 Improved Biointerrogation for a Better Understanding *13*
 2.11 Crossing the Structure–Function Threshold *14*
 2.12 Living Implants for a Living Matrix *15*
 2.13 Taming the Nanointerface *15*
 2.14 Where are We Now? *16*
 2.15 Where will the Revolution Take Us? *16*
 2.16 Conclusions *17*
 References *18*

3 Nanomedicine Activities in the United States and Worldwide 21

Carlotta Borsoi, Joy Wolfram, and Mauro Ferrari

- 3.1 Drug Delivery 22
 - 3.1.1 Strategies for Localized Delivery of Nanoparticles 23
 - 3.1.1.1 Physical Targeting 24
 - 3.1.1.2 Biomaterials 25
 - 3.1.1.3 Molecular Targeting 26
 - 3.1.1.4 External Activation 26
 - 3.1.2 Next-generation Drug Delivery Vehicles 27
 - 3.1.2.1 Sequential Drug Delivery 27
 - 3.1.2.2 Amplified Drug Delivery 29
 - 3.1.2.3 Biomimicry 29
 - 3.1.3 Implantable Devices 30
- 3.2 Diagnostics 31
- 3.3 Scaffolds 33
 - 3.3.1 Bone Tissue Regeneration 34
 - 3.3.2 Skin Regeneration 35
 - 3.3.3 Nerve Regeneration 36
- 3.4 Clinically Approved Nanoproduts 37
- References 39

Part Two Leading Cause of Death: Cardiovascular Diseases 51

4 Challenges in Cardiovascular Treatments Using Nanotechnology-Based Approaches 53

Till Saxer and Margaret N. Holme

- 4.1 Introduction 53
- 4.2 Unmet Needs in Cardiology 54
 - 4.2.1 Nanomaterials for Medical Applications 55
 - 4.2.2 Nanotechnology Applied to Medicine: A New Medical Discipline for Cardiology? 55
 - 4.2.3 Nano Approaches for Therapeutic Problems 56
 - 4.2.4 Awareness of Risks Introducing Nanotechnology to Patient Treatment 57
 - 4.2.5 Decisional Analysis in Nanomedicine Development 57
- 4.3 Nanoparticles for Treatment of CVD 58
 - 4.3.1 Delivery of Nitric Oxide Small-Molecule Donors 58
 - 4.3.2 PLGA-based Nanoparticles for Gene Delivery 59
 - 4.3.3 Perfluorocarbon Nanoparticles 60
 - 4.3.4 Targeting Vessel Geometry: a Physics-based Approach 60
 - 4.3.5 Nanoparticles Endogenous to Atherosclerosis Pathology 62
- 4.4 Nanotherapeutics in Surgical Interventions 62
 - 4.4.1 Nanoparticles in Drug-eluting Stents 63
 - 4.4.2 Nanopatterning to Improve Stent Integration 64

4.4.3	Nanoparticle Alternatives to Stents	65
4.5	Conclusions	65
	References	66
5	Smart Container for Targeted Drug Delivery	71
	<i>Andreas Zumbuehl</i>	
5.1	Introduction	71
5.2	Liposomes	72
5.2.1	General Characteristics	72
5.2.2	Release of Vesicle-Entrapped Molecules	74
5.2.2.1	Temperature as Trigger	74
5.2.2.2	Ultrasound as Trigger	75
5.2.2.3	Enzymes as Trigger	75
5.2.2.4	pH Changes as Trigger	75
5.2.2.5	Redox Reactions as Trigger	75
5.2.2.6	Photoreactions as Trigger	75
5.2.2.7	Shear Stress as Trigger	76
5.3	Shear Forces and Vesicles	76
5.3.1	Influence of Shear Forces on Vesicles	76
5.3.2	Shear Force-Responsive Vesicles	77
5.4	Conclusions	79
	References	79
6	Human Nano-Vesicles in Physiology and Pathology	83
	<i>Arun Cumpelik and Jürg A. Schifferli</i>	
6.1	Introduction	83
6.2	Nomenclature and Definition	84
6.3	Stimulus for Vesicle Release	85
6.4	Overview of Extracellular Vesicle Biology	86
6.5	NVs of Polymorphonuclear Leukocytes	88
6.6	Erythrocyte NVs	89
6.7	Platelet NVs	91
6.8	Conclusions	92
	Acknowledgment	93
	References	93
7	Challenges and Risks of Nanotechnology in Medicine: An Immunologist's Point of View	97
	<i>János Szebeni</i>	
7.1	Introduction	97
7.2	The Immune Stimulatory Vicious Cycle	98
7.3	The Cause of Immune Recognition of Nanomedicines: Similarity to Viruses	100
7.4	Processes in the Immune Stimulatory Vicious Cycle	101
7.4.1	Complement Activation-Related Pseudoallergy	101

7.4.1.1	Definition and Basics	101
7.4.1.2	Historic Leads	101
7.4.1.3	Foundation of the Concept	104
7.4.1.4	Prevalence, Symptoms, and Features	104
7.4.1.5	Mechanism	105
7.4.2	Immunogenicity and Formation of Antidrug Antibodies	106
7.4.3	Accelerated Blood Clearance (ABC Phenomenon)	107
7.4.3.1	Essentials and Background	107
7.4.3.2	The Immunogenicity of PEG-Conjugated Nanomedicines	107
7.4.4	Mechanism of PEG Immunogenicity	108
7.5	Particle Features Influencing the Immune Side Effects of Nanomedicines	109
7.6	Experimental Analysis of the Adverse Immune Effects of Nanomedicines	110
7.6.1	Measurement of C Activation	110
7.6.2	Prediction of Immunogenicity	110
7.6.3	Prediction of CARPA	111
7.7	Decision Tree to Guide the Evaluation of the CARPAgenic Potential of Nanomedicines	113
7.8	Outlook	114
	References	114

Part Three Second Most Common Cause of Death: Cancer 125

8 Challenges of Applying Targeted Nanostructures with Multifunctional Properties in Cancer Treatments 127

Jean-Luc Coll and Jungyoon Choi

8.1	Introduction	127
8.2	Enhanced Permeability and Retention Effect	128
8.2.1	Biological Point of View	128
8.2.2	Biophysical Perspective	129
8.3	Physicochemical Factors that Influence NP Passive Properties	129
8.3.1	Influence of the Size of the NP	130
8.3.2	Surface Modification and Opsonization	131
8.3.3	Electric Charge	133
8.3.4	Density of Ligands	134
8.4	Targeted NPs	134
8.4.1	Choice of Target Receptor	135
8.4.2	Targeting Folate Receptor Using Folic Acid as an Example of a Small Ligand	135
8.4.2.1	Folic Acid Receptor-Targeted NPs for Drug Delivery	136
8.4.2.2	Folic Acid Receptor-Targeted NPs as Contrast Agents	137
8.4.3	Targeting Integrin with Peptides	138

8.4.3.1	RGD-Targeted Gold NPs	139
8.4.4	Protein-Targeted NPs	141
8.4.4.1	Targeting Transferrin Receptor	141
8.4.4.2	Targeting the Epithelial Growth Factor Receptor	143
8.5	Conclusions	143
	Acknowledgments	144
	References	145
9	Highly Conformal Radiotherapy Using Protons	157
	<i>Antony John Lomax</i>	
9.1	Introduction	157
9.1.1	Principles of Radiotherapy	157
9.1.2	Radiotherapy with X-Rays	157
9.1.3	Radiotherapy Using Protons	159
9.2	Proton Physics	161
9.2.1	Energy Loss	161
9.2.2	Multiple Coulomb Scattering	161
9.2.3	Nuclear Interactions and Secondary Particles	162
9.2.4	Linear Energy Transfer and Relative Biological Effectiveness	163
9.2.5	Density Heterogeneities	163
9.2.6	Generating High-Energy Proton Beams	164
9.2.6.1	Cyclotron	164
9.2.6.2	Synchrotrons	165
9.3	Delivering Proton Therapy	165
9.3.1	Imaging and Treatment Planning	165
9.3.2	Passive Scattering	166
9.3.2.1	Spread-out Bragg Peak	166
9.3.2.2	Single and Double Scattering	167
9.3.2.3	Collimators and Compensators	168
9.3.2.4	Passive Scattering in Practice	168
9.3.3	Pencil Beam Scanning	169
9.3.3.1	Principle of PBS	169
9.3.3.2	PBS versus Passive Scattering	170
9.3.4	Treatment Gantries	171
9.4	Clinical Applications	172
9.4.1	Selected Clinical Indications	172
9.4.1.1	Uveal Melanoma	172
9.4.1.2	Skull-Base Chordomas	174
9.4.1.3	Ependymoma	176
9.5	The Future of Proton Therapy	177
9.5.1	Future is PBS	177
9.5.2	Current and Future Technological Developments	178
9.5.2.1	Treatment Delivery	178
9.5.2.2	Treatment Efficiency	179

9.5.2.3	In-Room/Onboard 3D Imaging and Adaptive Therapy	180
9.5.3	Clinical Future of Proton Therapy	182
9.6	Is There a Role for Nanotechnology in Proton Therapy?	183
9.6.1	Tumor Imaging	184
9.6.2	Dose Enhancement	184
9.6.3	Nanodosimetry	185
9.6.4	Summary	186
	References	186
10	Self-Organization on a Chip: From Nanoscale Actin Assemblies to Tumor Spheroids	191
	<i>Cora-Ann Schoenenberger and Thomas Pfohl</i>	
10.1	Introduction	192
10.2	Microfluidic Cell Culture	197
10.3	Self-Regulated Loading of Cells into Microchambers	197
10.4	2D Cell Culture in Microfluidics	200
10.5	Expanding Microfluidic Cell Culture to the Third Dimension	200
10.6	Microfluidic Biomimetic Models of Cancer	204
10.7	Future Perspectives	204
	Acknowledgments	205
	References	205
11	The Nanomechanical Signature of Tissues in Health and Disease	209
	<i>Daphne O. Asgeirsson, Philipp Oertle, Marko Loparic, and Marija Plodinec</i>	
11.1	Summary	209
11.2	Tissue Mechanics Across Length Scales	210
11.3	Atomic Force Microscopy (AFM) in Cell and Tissue Biology	211
11.3.1	Basic Operating Principles of AFM	211
11.3.2	Scale Dependency and Resolution	212
11.3.3	AFM in Cell Biology	215
11.4	The Nanomechanical Signature of Articular Cartilage	218
11.4.1	Articular Cartilage Composition and Function	218
11.4.2	The Nanomechanics of Articular Cartilage	219
11.4.3	The Nanomechanical Signature of Osteoarthritis	221
11.5	The Nanomechanical Signature of Mammary Tissues	224
11.5.1	Mammary Gland Composition and Mechanics	224
11.5.2	The Nanomechanical Signature of Breast Cancer	225
11.6	AFM – The Diagnostic and Prognostic Tool of the Future	229
	Acknowledgments	232
	Competing Financial Interests	232
	References	232

**Part Four Most Common Diseases: Caries, Musculoskeletal Diseases,
Incontinence, Allergies 241**

**12 Revealing the Nano-Architecture of Human Hard and Soft Tissues by
Spatially Resolved Hard X-Ray Scattering 243**

Hans Deyhle and Bert Müller

- 12.1 Introduction 243
- 12.2 Spatially Resolved Hard X-Ray Scattering 244
 - 12.2.1 Introductory Remarks on X-Ray Scattering 244
 - 12.2.2 Experimental Setup for X-Ray Scattering 246
 - 12.2.3 Two-Dimensional Scanning Small-Angle X-Ray Scattering 248
 - 12.2.4 Scattering Pattern Analysis 249
 - 12.2.5 Tissue Preparation 250
- 12.3 Nanoanatomy of Human Hard and Soft Tissues 251
 - 12.3.1 Human Tooth 251
 - 12.3.2 Femoral Head 254
 - 12.3.3 Breast Tumor 256
 - 12.3.4 Brain Tissue 256
- 12.4 Conclusions and Outlook 259
- References 259

13 Regenerative Dentistry Using Stem Cells and Nanotechnology 263

Thimios A. Mitsiadis and Giovanna Orsini

- 13.1 Introduction 263
- 13.2 Repair of Dental Tissues 264
- 13.3 Dental Stem Cells and Their Regenerative Potential 265
- 13.4 Regenerative Dentistry 267
- 13.5 Nanotechnology in Dentistry 269
- 13.6 Nanoscale Surface Modifications of Dental Biomaterials 270
 - 13.6.1 Approaches for Nanoscale Surface Modification in
Dental Implants 270
 - 13.6.2 Biological Surfaces Principles 271
 - 13.6.3 Cellular Responses to Nanostructured Surfaces 272
 - 13.6.4 Clinical Applications of Nanostructured Dental Implants 273
 - 13.6.5 Nanomodifications of Bone Replacements Materials 275
 - 13.6.6 Nanofillers in Dental Restorative Materials 276
 - 13.6.7 Nanoscale Modification in the Treatment of Dentin Hypersensitivity
and Enamel Remineralization 278
- 13.7 Concluding Remarks 279
 - Acknowledgments 280
 - References 280

14 Nanostructured Polymers for Medical Applications 293

Prabitha Urwyler and Helmut Schift

- 14.1 Introduction 293

14.1.1	Nanostructured Polymers – A Promising Approach in Biomedical Applications	293
14.1.2	Strategies for Creation of Surface Nanotopographies	294
14.2	Applications of Nanostructures	295
14.2.1	Which Nanoeffects Will Be Exploited for Biomedical Applications?	296
14.2.1.1	Combined Effects	298
14.2.1.2	Cell Proliferation and Differentiation	298
14.2.1.3	Protein Nanopattern	300
14.2.2	Mimicking Nature	300
14.2.3	Gecko-Inspired Bandage as an Example	301
14.3	Processes for Generation of Nanotopographies	301
14.3.1	Top-Down Manufacturing by Origination, Tooling, Replication	302
14.3.2	Bottom-Up Manufacturing By Self-Organization and Surface Postprocessing	303
14.4	Surface Patterning of Microcantilevers Using Mold Inlays	303
14.5	Surface Patterning Using Plasma Etching	306
14.6	Cell Response to Surface Patterning	308
14.7	Conclusion	309
	References	310
15	Nanotechnology in the Treatment of Incontinence	315
	<i>Vanessa Leung and Christian Gingert</i>	
15.1	Urinary Incontinence	316
15.1.1	Urinary Incontinence Etiology	316
15.1.2	Urinary in-/Continence Assessment	316
15.1.3	Physics of Urinary Continence	318
15.1.4	Tissue Engineering and Sling Material for Sphincter Regeneration	319
15.2	Fecal Incontinence	321
15.2.1	Fecal Incontinence Etiology	321
15.2.2	Physics of Fecal Continence	321
15.2.3	Fecal in-/Continence Assessment	322
15.2.4	Tissue Engineering for Sphincter Regeneration	323
15.2.5	Dielectric Elastomer Actuators for Sphincter Replacement	324
	References	327
16	Nanomedicine in Dermatology: Nanotechnology in Prevention, Diagnosis, and Therapy	329
	<i>Kathrin Scherer Hofmeier and Christian Surber</i>	
16.1	Introduction	329
16.2	Nature of Nanoparticles	330
16.2.1	Soft Particles	330
16.2.2	Rigid Particles	331
16.2.3	Surface Functionalization	332
16.2.4	Formulations with Nanoparticles	333

16.3	Absorption of Nanoparticles through Skin	333
16.3.1	Absorption Pathways	333
16.3.2	Risk and Safety Considerations	335
16.4	Nanoparticles in Prevention, Diagnosis, and Therapy	336
16.4.1	Prevention	336
16.4.1.1	Antisepsis	336
16.4.1.2	Photoprotection, Color, and Light Reflectance Control	337
16.4.1.3	Preventive Care	338
16.4.1.4	Odor Neutralizers	338
16.4.1.5	Vaccines	338
16.4.2	Diagnosis and Monitoring	338
16.4.3	Therapy	340
16.4.3.1	Sebaceous Gland Disorders	340
16.4.3.2	Hair Disorders	340
16.4.3.3	Inflammatory Disorders	341
16.4.3.4	Cancer	341
16.4.3.5	Surgery	343
16.5	Regulatory Issues	344
16.6	Public Perception of Nanoparticles in Topicals	344
16.7	Conclusions and Future Perspectives	345
	References	347

Part Five Benefiting Patients 357

17	Therapeutic Development and the Evolution of Precision Medicine	359
	<i>Gareth D. Healey and R. Steven Conlan</i>	
17.1	Origins of Nanomedicine	359
17.2	Global Nanomedicine Market	360
17.3	Nanomedicine Cabinet	361
17.4	Application of Nanomedicine – A Paradigm Shift	365
17.5	Targeted Drug Discovery and the Human Kinome	367
17.6	Translation from Discovery to the Clinic	369
17.7	Evolution of Kinase Inhibitors	370
17.8	Nanoparticle Delivery	372
17.9	Conclusions	374
	References	374
18	Benefit from Nanoscience and Nanotechnology: Benefitting Patients	379
	<i>Bert Müller and Marcel H. Van de Voorde</i>	
	Index	383

Nanomedicine: Present Accomplishments and Far-Reaching Promises

The symbolic dawn of nanotechnology is often ascribed to Richard Feynman's address to the American Physical Society in 1959: "There is plenty of room at the bottom.." Possible applications to medicine rapidly appeared as of major importance encompassing *in vitro* diagnosis, *in vivo* imaging, and therapeutics. It has been, however, necessary to wait until 1995 to have the first nanodrug approved by the US Food and Drug Administration – a liposomal formulation of doxorubicin termed Doxil®. At present, there are over 300 nanodrugs in various stages of clinical development. All of them, that have been already approved, rely on passive targeting: These compounds are accumulated in tumor tissue due to the existence of leaky, abnormally fenestrated blood vessels and also due to altered lymphatic circulation (EPR (enhanced permeability and retention effect)). Nanocarriers conjugated with antibodies or physiological ligands and thus specifically targeted to cells expressing the corresponding markers are the next step in the development of nanotherapeutics. Such drugs are expected to display a markedly increased therapeutic index, that is, increased effect on tumor tissue and decreased general toxicity. Several of them are now in the late stages of clinical studies and should become available soon. Future developments include theranostics and personalized nanomedicine. Theranostics consist in the presence of therapeutic and imaging compounds in the same carriers specifically targeted to tumor cells. A major advantage of this technology would be the possibility of noninvasive monitoring of early response to therapy and thus to rapid adaptation of the treatment. Personalized nanomedicine will allow the selection of nanodrugs specifically for each patient according to molecular markers ("-omics" data). In this respect, RNA interference seems a promising approach. In parallel to this progress, in diagnostics and therapy, it will be necessary to develop toxicology. The toxicity of a compound changes markedly when the latter is reduced at the nanometer scale. Besides toxicity, due to their shape – "asbestos-like" properties of carbon nanotubes – nanoparticle detrimental effects derive from generation of reactive oxygen species, cellular structure disruption, and immunological reactions. A great progress in the clinical development of

nanodrugs would be the availability of *in vitro* assays able to predict *in vivo* toxicity.

Nanoparticles are rapidly extending their use in industry: paints, electronics, tires, sport equipment, sunscreens, and so on. The possible toxicity of these compounds present in our environment should be examined. We should also keep in mind and try to prevent the possibility of most dreadful developments: the weaponization of the processes and compounds. The future of nanomedicine is obviously bright. It is bound to become one of our most important tools for diagnosis and therapy.

Member of the French Academy of Medicine

Edwin Milgrom

Part One
Introduction to Nanoscience in Medicine
of the Twenty-First Century

1

Challenges and Opportunities of Nanotechnology for Human Health

Bert Müller

*University of Basel, Department of Biomedical Engineering, Biomaterials Science Center,
Gewerbstrasse 14, 4123 Allschwil, Switzerland*

Medical doctors have a wide variety of experiences with patients. Therefore, they are generally fast in the evaluation of the entire human body. For example, looking at the morphology of the human body, they can identify the chronic inflammatory disease of the axial skeleton, termed ankylosing spondylitis, previously known as Bekhterev's disease. For many natural scientists and engineers, these abilities are fascinating and surprising, at once.

For the diagnosis of an increasing number of diseases, however, a more detailed evaluation, for example, on the basis of radiological data, is necessary. The amount of high-resolution data obtained is huge and usually overburdens the medical experts. Interdisciplinary cooperation with computer scientists to (semi)automatically analyze the imaging data becomes more and more common. These assessments are often expensive and time-consuming. Nonetheless, the available clinical imaging modalities even with the best spatial resolution do not reach the resolution needed to visualize individual biological cells with sizes of about 10 μm . To this end, it appears dubious, why patients can benefit from nanotechnology.

Reading the instruction leaflets of currently available sun crèmes or sensitive toothpastes, we realize, however, that nanotechnology has reached our daily routine. This book will hardly deal with these well-established, systemic applications, we have known from pharmacy for decades, but with the impact of nanotechnology on dedicated future therapies for the most important diseases.

The leading cause of death in our society relates to cardiovascular diseases [1]. Therefore, the first part of this book, which consists of four chapters from medical experts, that is, cardiologist, internist, immunologist, and natural scientists, targets current research activities toward nonsystemic treatments. For example, nitroglycerin is currently administered to widen the constricted atherosclerotic arteries in a systemic fashion. The vasodilator widens all arteries and veins with serious side effects, including a drastic blood pressure drop. Therefore, the nitroglycerin dose has to be kept limited. Specific biomarkers

for this prevalent inflammation do not exist. Consequently, researchers proposed to exploit the wall shear stress increased at constricted arteries with respect to the healthy parts as purely physical trigger to release drugs from mechanosensitive containers or particles of nanometer size [2,3]. These nanotechnology-based innovations are sweeping the established cardiovascular treatments, especially before the patients reach the operating room and endovascular devices for intra-arterial clot lysis, stent implantation, or arterial balloon dilatation could become effective [4].

Second most common cause of death is cancer. It is, therefore, not surprising that the second part of the book is dedicated to alternative diagnoses and treatments of cancer. Although one can cleverly combine pharmaceutical, surgical, and radiation treatments to heal patients, alternative strategies to fight against cancer are more than desirable. The four related chapters depict how contemporary methods and sophisticated materials can contribute to a reliable diagnosis and, more important, to powerful treatments of cancerous tissues even deeply inside the human body difficult to reach. Here, the deep understanding of the physical interactions between the probes such as photons or protons and the biological matter is essential for the selection and the future development of treatment strategies for the general public.

The third part of the book relates to the most common diseases, which are caries, musculoskeletal diseases, incontinence, and allergies. Although they often do not result in death, they massively influence our quality of life.

Caries is the most common infectious bacterial diseases in the world [5]. The disease first destroys the human enamel, which is a unique biologically ordered material with hydroxyapatite crystallites being organized into a fibrous continuum. In healthy state, it remains stable for decades and centuries or even millennia. Currently, no engineering process exists to biomimetically repair this unique biological material with a well-defined nanostructural organization. Therefore, the burden of dental caries lasts for a lifetime. Once the tooth structure is destroyed, it will usually need restoration and additional maintenance throughout life. In addition, the economic impact of such therapeutic approaches is enormous. The World Health Organization estimated that the dental treatment costs accounted for 5–10% of healthcare budgets in industrialized countries and additional costs are caused through absences from work [6,7]. So far, treatments rely on mechanical replacement of decayed tissue by inert biomaterials such as isotropic polymers or composites. Recently, the analysis of the healthy and diseased crowns down to the nanometer scale has led to the necessary anatomical knowledge to develop biomimetic dental fillings, which contain elongated nanostructures with the orientations present in dentin and enamel [8]. Furthermore, the detailed analysis of the caries pathology using X-ray scattering has shown that while bacterial processes dissolve the minerals in enamel and dentin, the dentinal collagen network remains unaffected, enabling the development of treatments to remineralize the dentin [9,10].

The musculoskeletal system demands increasingly frequent treatments with metallic load-bearing implants, which include artificial hips, knees, and dental implants. In general, these metals integrate well into the bone because the sand-blasted and etched oxide surface contains a multiplicity of features on the micro- and nanometer scale, which exhibit similarities to the nanometer-size minerals in bone. Therefore, it has been stated that the morphology of the implant's surface tends to have a greater effect than chemical patterns, when both chemical patterns and topographic ones are offered to biological cells [11]. The vital role of the nanostructures in avoiding inflammatory reactions and in reaching cytocompatibility was demonstrated using nanopyramids naturally formed in heteroepitaxy of semiconductors [12,13]. In contrast to metals, high-performance polymers are radiolucent and magnetic resonance imaging compatible, which allow the diagnostic examination of tissues in implant's vicinity. Only recently, the systematic polymer structuring on the nanometer scale for centimeter-size implants was explored [14]. It is relatively easy to produce micro- and nanostructures with a preferential orientation, which better mimic the anisotropy of the bony tissues within our body [15]. Therefore, one can reasonably expect that polymeric load-bearing implants will be employed in near future at least for dedicated cases.

The aging of our society has led to the increasing prevalence of social and economic burdening by age-related diseases, including urinary and fecal incontinence. In comparatively simple cases, conservative therapy is successful. Surgical therapy is advisable for more complex cases, where the extent of surgery depends on the severity. In severe cases, artificial sphincter systems are applied, which currently rely on fluid-filled cuffs. So far, they are not part of everyday surgical treatments owing to the large number of complications, including wound infection, postoperative pain, and consecutive resurgeries. One of the main drawbacks is the constant pressure acting on the hollow organ. The natural counterpart, however, adapts to external factors such as climbing stairs or resting in bed, so that the function is guaranteed and the tissue can regenerate. Hence, sensor-controlled devices with the necessary time response have to be developed [16]. As dielectric elastomer actuators (DEA) not only provide the necessary forces, strains, and response time but can also simultaneously be operated as sensors, these artificial muscles have a huge potential to become the basis of future active implants [17]. There are, however, several challenges to be solved, mainly related to the high voltages required to drive micrometer-thin DEA. Sandwiched nanometer-thin elastomer films with ultrathin compliant electrodes have to be made available to fabricate biomimetic artificial sphincters and finally to successfully treat incontinence.

The book *Nanotechnology for Human Health* should promote the prosperous use of nanotechnology in prevention, diagnosis, and therapy of the most relevant diseases of our century. It should comparably become a tool for research-interested medical doctors as well as natural scientists and engineers with a strong affinity to support curing patients [18,19]. In this manner, patients concerned will benefit from this collaborative initiative of an interdisciplinary team of researchers.

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