

CLINICAL APPLICATIONS OF MAGNETIC NANOPARTICLES

EDITED BY **Nguyễn T. K. Thanh**



CRC Press
Taylor & Francis Group

Clinical Applications of Magnetic Nanoparticles



Taylor & Francis

Taylor & Francis Group

<http://taylorandfrancis.com>

Clinical Applications of Magnetic Nanoparticles

Design to Diagnosis
Manufacturing to Medicine

Edited by
Nguyễn T. K. Thanh



CRC Press

Taylor & Francis Group
Boca Raton London New York

CRC Press is an imprint of the
Taylor & Francis Group, an **informa** business

CRC Press
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742

© 2018 by Taylor & Francis Group, LLC
CRC Press is an imprint of Taylor & Francis Group, an Informa business

No claim to original U.S. Government works

Printed on acid-free paper

International Standard Book Number-13: 978-1-138-05155-3 (Hardback)

This book contains information obtained from authentic and highly regarded sources. Reasonable efforts have been made to publish reliable data and information, but the author and publisher cannot assume responsibility for the validity of all materials or the consequences of their use. The authors and publishers have attempted to trace the copyright holders of all material reproduced in this publication and apologize to copyright holders if permission to publish in this form has not been obtained. If any copyright material has not been acknowledged, please write and let us know so we may rectify in any future reprint.

Except as permitted under U.S. Copyright Law, no part of this book may be reprinted, reproduced, transmitted, or utilized in any form by any electronic, mechanical, or other means, now known or hereafter invented, including photocopying, microfilming, and recording, or in any information storage or retrieval system, without written permission from the publishers.

For permission to photocopy or use material electronically from this work, please access www.copyright.com (<http://www.copyright.com/>) or contact the Copyright Clearance Center, Inc. (CCC), 222 Rosewood Drive, Danvers, MA 01923, 978-750-8400. CCC is a not-for-profit organization that provides licenses and registration for a variety of users. For organizations that have been granted a photocopy license by the CCC, a separate system of payment has been arranged.

Trademark Notice: Product or corporate names may be trademarks or registered trademarks, and are used only for identification and explanation without intent to infringe.

Library of Congress Cataloging-in-Publication Data

Names: Thanh, Nguyen T. K. (Thi Kim), editor.
Title: Clinical applications of magnetic nanoparticles / [edited by] Nguyen T.K. Thanh.
Description: Boca Raton : Taylor & Francis, 2018. | Includes bibliographical references and index.
Identifiers: LCCN 2017045414 | ISBN 9781138051553 (hardback : alk. paper)
Subjects: | MESH: Magnetite Nanoparticles--therapeutic use | Drug Carriers--therapeutic use | Diagnostic Imaging
Classification: LCC R857.N34 | NLM QT 36.5 | DDC 610.28--dc23
LC record available at <https://lccn.loc.gov/2017045414>

Visit the Taylor & Francis Web site at
<http://www.taylorandfrancis.com>

and the CRC Press Web site at
<http://www.crcpress.com>

This book is dedicated to my dear parents, who encouraged me at a very young age to be independent and allowed me to fly as far as I wish.



Taylor & Francis

Taylor & Francis Group

<http://taylorandfrancis.com>

Contents

Foreword	xi
Preface.....	xiii
Acknowledgements	xv
Editor	xvii
Foreword Author.....	xix
Contributors	xxi

SECTION I *Fabrication, Characterisation of MNPs*

Chapter 1	Controlling the Size and Shape of Uniform Magnetic Iron Oxide Nanoparticles for Biomedical Applications ...	3
	<i>Helena Gavilán, Maria Eugênia Fortes Brollo, Lucía Gutiérrez, Sabino Veintemillas-Verdaguer and María del Puerto Morales</i>	
Chapter 2	Magnetic Nanochains: Properties, Syntheses and Prospects.....	25
	<i>Irena Markovic-Milosevic, Vincent Russier, Marie-Louise Saboungi and Laurence Motte</i>	
Chapter 3	Carbon-Coated Magnetic Metal Nanoparticles for Clinical Applications	43
	<i>Martin Zeltner and Robert N. Grass</i>	
Chapter 4	Bioinspired Magnetic Nanoparticles for Biomedical Applications.....	53
	<i>Changqian Cao and Yongxin Pan</i>	

SECTION II *Biofunctionalisation of MNPs*

Chapter 5	Main Challenges about Surface Biofunctionalization for the <i>In Vivo</i> Targeting of Magnetic Nanoparticles	77
	<i>Laurent Adumeau, Marie-Hélène Delville and Stéphane Mornet</i>	
Chapter 6	Experimental Considerations for Scalable Magnetic Nanoparticle Synthesis and Surface Functionalization for Clinical Applications	97
	<i>Alec P. LaGrow, Maximilian O. Besenhard, Roxanne Hachani and Nguyễn T. K. Thanh</i>	
Chapter 7	Magnetic Polymersomes for MRI and Theranostic Applications.....	121
	<i>Adeline Hannecart, Dimitri Stanicki, Luce Vander Elst, Robert N. Muller and Sophie Laurent</i>	
Chapter 8	Ultrasmall Iron Oxide Nanoparticles Stabilized with Multidentate Polymers for Applications in MRI	139
	<i>Jung Kwon (John) Oh and Marc-André Fortin</i>	
Chapter 9	Encapsulation and Release of Drugs from Magnetic Silica Nanocomposites	161
	<i>Damien Mertz and Sylvie Bégin-Colin</i>	

SECTION III *In-Vitro Application of MNPs*

Chapter 10	Current Progress in Magnetic Separation-Aided Biomedical Diagnosis Technology	175
	<i>Sim Siong Leong, Swee Pin Yeap, Siew Chun Low, Rohimah Mohamud and JitKang Lim</i>	
Chapter 11	Magnetic Separation in Integrated Micro-Analytical Systems	201
	<i>Kazunori Hoshino</i>	
Chapter 12	Magnetic Nanoparticles for Organelle Separation	229
	<i>Mari Takahashi and Shinya Maenosono</i>	
Chapter 13	Magnetic Nanoparticle-Based Biosensing	247
	<i>Kai Wu, Diqing Su, Yinglong Feng and Jian-Ping Wang</i>	

SECTION IV *In-Vivo Application of MNPs*

Chapter 14	Immunotoxicity and Safety Considerations for Iron Oxide Nanoparticles.....	273
	<i>Gary Hannon, Melissa Anne Tutty and Adriele Prina-Mello</i>	
Chapter 15	Impact of Core and Functionalized Magnetic Nanoparticles on Human Health.....	289
	<i>Bella B. Manshian, Uwe Himmelreich and Stefaan J. Soenen</i>	
Chapter 16	Magnetic Nanoparticles for Cancer Treatment Using Magnetic Hyperthermia.....	305
	<i>Laura Asín, Grazyna Stepień, María Moros, Raluca Maria Fratila and Jesús Martínez de la Fuente</i>	
Chapter 17	Nanoparticles for Nanorobotic Agents Dedicated to Cancer Therapy	319
	<i>Mahmood Mohammadi, Charles Tremblay, Ning Li, Kévin Gagné, Maxime Latulippe, Maryam S. Tabatabaei and Sylvain Martel</i>	
Chapter 18	Smart Nanoparticles and the Effects in Magnetic Hyperthermia <i>In Vivo</i>	331
	<i>Ingrid Hilger</i>	
Chapter 19	Noninvasive Guidance Scheme of Magnetic Nanoparticles for Drug Delivery in Alzheimer's Disease	343
	<i>Ali Kafash Hoshidar, Tuan Anh Lea, Faiz Ul Amin, Xingming Zhang, Myeong Ok Kim and Jungwon Yoon</i>	
Chapter 20	Design, Fabrication and Characterization of Magnetic Porous PDMS as an On-Demand Drug Delivery Device.....	365
	<i>Ali Shademani, Hongbin Zhang and Mu Chiao</i>	
Chapter 21	Magnetic Particle Transport in Complex Media	381
	<i>Lamar O. Mair, Aleksandar N. Nacev, Sagar Chowdhury, Pavel Stepanov, Ryan Hilaman, Sahar Jafari, Benjamin Shapiro and Irving N. Weinberg</i>	

Chapter 22 Magnetic Nanoparticles for Neural Engineering	395
<i>Gerardo F. Goya and Vittoria Raffa</i>	
Chapter 23 Radionuclide Labeling and Imaging of Magnetic Nanoparticles	411
<i>Benjamin P. Burke, Christopher Cawthorne and Stephen J. Archibald</i>	
Chapter 24 Red Blood Cells Constructs to Prolong the Life Span of Iron-Based Magnetic Resonance Imaging/Magnetic Particle Imaging Contrast Agents <i>In Vivo</i>	431
<i>Antonella Antonelli and Mauro Magnani</i>	
Chapter 25 Stimuli-Regulated Cancer Theranostics Based on Magnetic Nanoparticles	451
<i>Yanmin Ju, Shiyan Tong and Yanglong Hou</i>	
 SECTION V <i>Good Manufacturing Practice</i>	
Chapter 26 Good Manufacturing Practices (GMP) of Magnetic Nanoparticles	475
<i>Nazende Günday Türeli and Akif Emre Türeli</i>	
Index	485



Taylor & Francis

Taylor & Francis Group

<http://taylorandfrancis.com>

Foreword

This book builds on the demand created by Professor Thanh's earlier volume *Magnetic Nanoparticles: From Fabrication to Clinical Applications*. The editor is a well-known and highly respected research scientist, well versed in many aspects of nanoscience and especially in this particular topic.

In the earlier volume, the foundations for making magnetic nanoparticles were clearly set out and it became apparent that another book would be needed to give scientists and clinicians a guide to what is happening in this field as the subject translates from the laboratory towards clinical practice. Inevitably, there is a very slight overlap with the earlier volume, and the first four chapters of this new book cover some new synthesis routes not covered in the earlier volume, which include methods of varying the particle size and shape, of the creation of chains of nanoparticles and the coating of metal particles by carbon and using bio-inspired methods for synthesis. These chapters, like many others in the book, deal with the potential applications and give very fair appraisals of the strengths and weaknesses of their approaches. Professor Thanh is to be congratulated in urging the many authors to be as objective as possible!

Surface functionalization is the key to most applications of nanoparticles of all types, and this is especially important here. There are several chapters devoted to the topic, and it recurs in many of the specific application chapters. It is very helpful to have available the many approaches that are in use in one book. Magnetic particles have the potential to enhance contrast in MRI images, and this topic receives detailed attention from several authors.

Magnetic particles hold the promise for separation of biomolecules and enhancing biosensing. There are chapters covering all of the current aspects of this very important application, both *in vitro* and *in vivo*. This enables the manipulation and sorting of cells and internal components of cells, such as mitochondria, and it is an area in which we will see increasing utility.

Health issues are always paramount in any use of nanotechnology, and several chapters deal with this with specific regard to the magnetic nanoparticles that are being developed for medical applications. The subject of the fate and possible toxicity of all types of nanoparticles is still debated and we are now getting a much more clear and objective view of these issues.

Magnetic hyperthermia is receiving a lot of attention because it has the possibility of offering a purely physical, nonchemical method of destroying cancerous cells. Added to this is the magnetically guided therapy afforded by directing a drug-loaded particle precisely to a site in the body, and this raises the question about the transport of nanoparticles through porous body tissue, which is dealt with in a complete chapter.

Imaging is important in medicine, and additional modalities can be added to particles designed for magnetic resonance imaging (MRI), and this aspect is described in several chapters and for various future clinical applications.

Finally, the considerations of Good Manufacturing Practice are discussed with respect to magnetic nanoparticles, and this is a useful chapter for all of the contemporary clinical applications of nanoparticles.

Having been asked to write this Foreword, I read the individual chapters and I found that it is very difficult to stop! Each set of specialist authors has produced a fascinating and informative review of their subject matter. This will render the book as a useful tool for learning about almost every aspect of magnetic nanoparticles for clinical application. It is therefore recommended for a wide range of readers, from students to research professors and medical practitioners, and it forms a good companion to Professor Thanh's earlier book.

Peter J. Dobson, OBE
The Queen's College, Oxford



Taylor & Francis

Taylor & Francis Group

<http://taylorandfrancis.com>

Preface

More than six years ago, when I wrote the preface for the book *Magnetic Nanoparticles: From Fabrication to Clinical Applications* (<http://www.crcpress.com/product/isbn/9781439869321>), it did not occur to me that I would write another one so soon. However, at every conference I attended, I saw the burgeoning research of magnetic nanoparticles (NPs). I could not help wanting to try to capture the most cutting-edge discovery and ever-expanding research in this field. With the success of the first book, it was a tall order to get this book right as well (e.g. being comprehensive, with 26 chapters, serving a wide audience from early-year research students to professors and being useful not only to practitioners but also to researchers who would like to join the field).

The current book is not overlapping with the first one, but complementary, and covers areas the first book did not, such as the extensive background and development of magnetic NPs (MNPs) as negative and positive contrast agents for magnetic resonance imaging. The 'Fabrication' part of the book covers different synthetic methods for iron oxide MNPs, the mechanism of NP formation, how to control the dimensions and morphology of NPs, which is essential for the optimization of their properties. New magnetic nanostructures, such as nanochains and carbon-coated magnetic metal NPs, as well as bio-inspired synthesis of MNPs are covered.

Very detailed strategies for *biofunctionalization* of MNPs, and their interaction with the biological environment, are beautifully covered. A new framework to experimentally take NP syntheses in the laboratory towards scalable manufacturing, including not only the synthesis but also surface modification, is covered to address the outstanding challenge of creating robust and reproducible syntheses of functionalized NPs. For the biofunctionalization of NPs, polymersomes and multidentate polymers are of particular interest for the stability they provide to the MNPs. Magnetic core–mesoporous silica shell composites with improved drug payloads and the ability to tune the drug release are presented.

In vivo applications, including high- and low-gradient magnetic separations with distinctive separation mechanisms, are discussed for biomedical diagnostics. Magnetic separation in integrated micro-analytical systems and magnetic separation of cellular organelles such as endosomes, exosomes and mitochondria are introduced. MNP-based biosensing with giant magnetoresistance biosensors and Hall sensors are reviewed.

Preceding *in vivo applications*, immunotoxicity and safety considerations for iron oxide NPs and the impact of MNPs on human health should be investigated. It is fascinating to see the idea of using nanorobots to navigate in multiscale complex vascular networks to deliver cancer therapy in addition to the extensive research on magnetic hyperthermia. MNPs used for drug delivery in Alzheimer's disease, as well as for on-demand drug delivery devices based on a magnetic sponge, which are transported in complex media, are presented. When magnetic cores are functionalized with molecules such as nerve growth factors or neuroprotective molecules, multifunctional devices can be developed for neurological diseases, specifically those based on the use of engineered MNPs applied to neuroprotection and neuroregeneration.

For *in vivo applications*, red blood cells were used as carriers for NP-based MRI and magnetic particle imaging contrast agents to prolong their circulation in the bloodstream. The advantages of nuclear imaging of radiolabeled MNPs for biomedical applications and roadmap for developing and imaging radiolabeled NPs are covered. Stimuli-regulated cancer theranostics based on MNPs such as internal stimuli-responsive NPs, including pH, reduction-sensitive NPs and external stimuli-inductive NPs, such as magnetic field- and light-controlled NPs, is also presented.

Finally, establishing large-scale good manufacturing practice (GMP) compliant NPs is the prerequisite to successfully translate the laboratory-scale synthesis to commercial products. The importance of continuous manufacturing methods enables the control of critical quality attributes with adjustment of production parameters, which are also closely monitored with in-process controls, are highlighted.

Similarly with the first book, the chapters were written by world-leading experts in the broad range of disciplines (e.g. physics, chemistry, biochemistry, biology, medicine, engineering and entrepreneurship). They not only present the most cutting-edge research for active scientists in the field but also provide the fundamental knowledge to enable students and other incoming researchers to take steps to translate their technologies to clinics.

Nguyễn T. K. Thanh, FRSC

Biophysics Group

Department of Physics and Astronomy

University College London

London, United Kingdom

Email: ntk.thanh@ucl.ac.uk



Taylor & Francis

Taylor & Francis Group

<http://taylorandfrancis.com>

Acknowledgements

First and foremost, I would like to thank my husband and wonderful children for allowing me to devote my time to editing this book.

I am privileged to have trust from colleagues in agreeing to spend their precious time in preparing very comprehensive chapters and then to have done their revision after reviewing to produce the highest quality ones.

I am indebted to many volunteer reviewers who provided their insightful comments and made the book valuable not only to people already working on magnetic nanoparticles for clinical application but also to wider communities.

My thanks to Dr. Alejandro Baeza García, Mr. Andreas Sergides, Prof. Andreas Tschope, Dr. Ángel del Pozo, Dr. Ángel Millán Escolano, Prof. Antoine Perreira, Dr. Aristides Bakandritsos, Dr. Beata Kalska-Szostko, Dr. Bernd Baumstümmler, Dr. Boris Polyak, Prof. Carlos Frederico de Gusmão Campos Geraldes, Prof. Christine Ménager, Dr. Christopher Adams, Dr. Claire Wilhelm, Dr. Cordula Grüttner, Prof. Daishun Ling, Dr. Damien Faivre, Prof. Daniel Horak, Dr. Dimitri Stanicki, Dr. Eleni K. Efthimiadou, Prof. Enrico Bergamaschi, Dr. Enza Torino, Prof. Erwann Guenin, Prof. Franca Bigi, Dr. Franck Couillard, Mr. Georgios Kasparis, Dr. Gurvinder Singh, Prof. Ian Prior, Prof. Igor Chourpa, Dr. Inge Katrin Herrmann, Prof. Ivo Safarik, Dr. Jean-Olivier Durand, Prof. Jeff W.M. Bulte, Prof. Jeffrey Chalmers, Dr. Jennifer Hall Grossman, Dr. Jordi Faraudo, Dr. Joseph Bear, Dr. Kazunori Shimizu, Prof. Ladislau Vakas, Dr. Li Zhang, Dr. Liliana Maria Pires Ferreira, Miss Lilin Wang, Dr. Maciej Zborowski, Prof. Manuel Ricardo Ibarra García, Dr. Maria Francesca Casula, Dr. Marijana Mionic, Dr. Marin Tadić, Dr. Nora M. Dempsey, Dr. Oliver Weber,

Dr. Olivier Sandre, Dr. Oliviero Gobbo, Prof. Oula Peña Medina, Miss Panagiota Chondrou, Dr. Penelope Bouziotis, Prof. Peter Dobson, Dr. Quoc Lam Vuong, Dr. Rafael Torres Martin De Rosales, Dr. Ralf Mundkowsky, Prof. Randall Erb, Miss Raquel Rodrigues, Dr. Ruxandra Gref, Prof. Samuel D. Bader, Dr. Sofia Lima, Dr. Spiridon V. Spirou, Dr. Stefanos Mourdikoudis, Prof. Sylvio Dutz, Dr. Tanya Prozorov, Dr. Touraj Ehtezazi, Dr. Vladan Kusigerski, Prof. Vladimir L. Kolesnichenko, Prof. Wilfried Weber and Dr. Yaowu Hao for their useful discussion on the book.

My special thanks to Prof. Jon Preece for helping me in deciding the title of this book to reflect its nature as a complementary volume to the first one. Also thanks to EU COST Action TD1402 Radiomag for many networking opportunities to discuss the book.

I would like to thank Barbara Glunn, Danielle Zarfati, Jonathan Achorn and their colleagues at CRC Press/Taylor & Francis who worked closely with me to publish this timely book.

I am ever thankful for the support from many wonderful scientists, engineers, clinicians and entrepreneurs around the world in this project. Your effort will surely push the research closer to meaningful applications that would one day save many more lives.

Nguyễn T. K. Thanh, FRSC

Biophysics Group

Department of Physics and Astronomy

University College London

London, United Kingdom

Email: ntk.thanh@ucl.ac.uk



Taylor & Francis

Taylor & Francis Group

<http://taylorandfrancis.com>

Editor



Nguyễn T. K. Thanh, FRSC, MInstP (<http://www.ntk-thanh.co.uk>) held a prestigious Royal Society University Research Fellowship (2005–2014). She was appointed a full professor in nanomaterials in 2013 at Biophysics Group, Department of Physics and Astronomy, University College London, UK. She leads a very dynamic group conducting cutting-edge *interdisciplinary and*

innovative research on the design and synthesis of magnetic and plasmonic nanomaterials for biomedical applications. A very strong feature of her research program is developing new chemical methods and, in collaboration with chemical engineers, producing the next generation of nanoparticles with very high magnetic moment and novel hybrid and multifunctional nanostructures. Detailed mechanistic studies of their formation by sophisticated and advanced analysis of the nanostructure allow tuning of the physical properties at the nanoscale; these can subsequently be exploited for diagnosis and treatment of various diseases. These studies are conducted to provide insight for future material design approaches. It will also help to identify the critical process parameters that can be manipulated in order to obtain the suitable physical properties for the intended applications.

She was the sole editor of the book *Magnetic Nanoparticles: From Fabrication to Clinical Applications* published by CRC Press/Taylor & Francis: <http://www.crcpress.com/product>

[/isbn/9781439869321](http://www.crcpress.com/product/isbn/9781439869321). In 2016, she was a guest editor of the Royal Society Interface Focus on “Multifunctional nanostructures for diagnosis and therapy of diseases.”

She has published over 80 peer-reviewed journal articles and book chapters with over 4500 citations so far. She has been a visiting professor at various universities in France, Japan, China and Singapore. She has been an invited speaker at over 200 institutes and scientific meetings. She has a leadership role in professional communities by chairing and organising 30 high-profile international conferences such as the American Chemistry Society symposia in 2018, 2012 and 2010; Royal Society of Chemistry UK Colloids Conferences in 2017, 2014 and 2011; European Material Research Society Symposia in 2016 and 2013; ICMAT Singapore in 2015 and 2013; Faraday Discussions in 2014, and being a member of advisory boards in Europe, the United States and Japan. She served in the Joint Committee of the Royal Society of Chemistry Colloid & Interface Science Group and the Society of Chemical Industry Colloid & Surface Chemistry Group (2008–2017). She is an elected member of The Royal Society of Chemistry Faraday Division Council and is currently serving on the Awards Committee and was a representative member of Joint Colloids Groups (2013–2016). She is a workgroup leader of EU COST Action TD1402 on Multifunctional Nanoparticles for Magnetic Hyperthermia and Indirect Radiation Therapy (RADIOMAG). She is a cochair of the 13th International Conference on the Scientific and Clinical Applications of Magnetic Carriers in June 2020, London, UK.



Taylor & Francis

Taylor & Francis Group

<http://taylorandfrancis.com>

Foreword Author



Professor Peter J. Dobson, OBE, BSc, MA (Oxon), PhD, C Phys, F Inst P, Member of the ACS, FRCS (The Queen's College, Oxford)

Peter has had a broad career covering a wide range of disciplines, from physics and chemistry to materials science and engineering. He has also worked in industry (Philips) as well as academia

(Imperial College and Oxford) and was responsible for creating and building the Begbroke Science Park for Oxford University. He has published over 190 papers and 32 patents. He has founded three companies and advised on the formation of eight more. He was the strategic advisor on nanotechnology to the Research

Councils in the UK (2009–2013) and has been on several Engineering and Physical Sciences Research Council (EPSRC) panels and committees. Peter currently sits on the EPSRC Strategic Advisory Board on Quantum Technology. He was awarded the Officer of the Order of the British Empire in 2013 in recognition of his contributions to science and engineering. He is currently a Principal Fellow at Warwick Manufacturing Group and a visiting professor at King's College London and University College London and chairs the Industrial Advisory Board of the Physics Department at Bristol University. He also chairs the Natural Environment Research Council Facility for Environmental Nanoscience Analysis and Characterization at Birmingham University. Peter delivers courses at graduate level in the areas of biosensors, nanotechnology, innovation, entrepreneurship and related topics and advises on innovation.



Taylor & Francis

Taylor & Francis Group

<http://taylorandfrancis.com>

Contributors

Laurent Adumeau

Centre for BioNano Interactions
School of Chemistry and Chemical Biology
University College Dublin
Dublin, Ireland

Faiz Ul Amin

Department of Biology and Applied Life Science
Gyeongsang National University
Jinju, Republic of Korea

Antonella Antonelli

Department of Biomolecular Sciences
University of Urbino Carlo Bo
Italy

Stephen J. Archibald

Department of Chemistry
and
Positron Emission Tomography Research Centre
University of Hull
Hull, United Kingdom

Laura Asín

Aragon Institute of Materials Science & CIBER-BBN
University of Zaragoza/CSIC
Zaragoza, Spain

Sylvie Bégin-Colin

Institut de Physique et Chimie des Matériaux de Strasbourg
Université de Strasbourg
Strasbourg Cedex, France

Maximilian O. Besenhard

Department of Chemical Engineering
University College London
London, United Kingdom

Maria Eugênia Fortes Brollo

Department of Energy, Environment & Health
Instituto de Ciencia de Materiales de Madrid (ICMM)
Consejo Superior de Investigaciones Científicas, CSIC
Madrid, Spain

Benjamin P. Burke

Department of Chemistry
and
Positron Emission Tomography Research Centre
University of Hull
Hull, United Kingdom

Changqian Cao

France-China Bio-Mineralization and Nano-Structures
Laboratory
and
Palaeomagnetism and Geochronology Laboratory
CAS Key Laboratory of Earth and Planetary Physics
Institute of Geology and Geophysics
Chinese Academy of Sciences
Beijing, China

Christopher Cawthorne

School of Life Sciences
and
Positron Emission Tomography Research Centre
University of Hull
Hull, United Kingdom

Mu Chiao

Department of Mechanical Engineering
University of British Columbia
Vancouver, Canada

Sagar Chowdhury

Weinberg Medical Physics, Inc.
North Bethesda, Maryland

Jesús Martínez de la Fuente

Aragon Institute of Materials Science & CIBER-BBN
University of Zaragoza/CSIC
Zaragoza, Spain

María del Puerto Morales

Department of Energy, Environment and Health
Instituto de Ciencia de Materiales de Madrid (ICMM)
Consejo Superior de Investigaciones Científicas, CSIC
Madrid, Spain

Marie-Hélène Delville

Institute for Condensed Matter Chemistry of Bordeaux
(ICMCB)
National Center for Scientific Research, CNRS
University of Bordeaux
Pessac, France

Yinglong Feng

The Center for Micromagnetics & Information Technologies
(MINT)
Department of Electrical & Computer Engineering
University of Minnesota
Minneapolis, Minnesota

Marc-André Fortin

Laboratory for Biomaterials in Imaging
 Department of Mining, Metallurgical and Materials Engineering
 and
 Centre de Recherche du Centre Hospitalier Universitaire de
 Québec (CR-CHUQ)
 Université Laval
 Québec, Canada

Raluca Maria Fratila

Aragon Institute of Materials Science & CIBER-BBN
 University of Zaragoza/CSIC
 Zaragoza, Spain

Kévin Gagné

Polytechnique Montréal
 Department of Computer and Software Engineering
 Institute of Biomedical Engineering
 Nanorobotics Laboratory
 Montréal, Canada

Helena Gavilán

Department of Energy, Environment and Health
 Instituto de Ciencia de Materiales de Madrid (ICMM)
 Consejo Superior de Investigaciones Científicas, CSIC
 Madrid, Spain

Gerardo F. Goya

Institute of Nanoscience of Aragón
 Department of Condensed Matter Physics
 University of Zaragoza
 Zaragoza, Spain

Robert N. Grass

Functional Materials Laboratory
 Institute for Chemical and Bioengineering
 Department of Chemistry and Applied Biosciences
 ETH Zurich
 Zurich, Switzerland

Lucía Gutiérrez

Instituto de Nanociencia de Aragón, INA
 Universidad de Zaragoza
 Zaragoza, Spain

Roxanne Hachani

Department of Physics and Astronomy
 University College London
 and
 UCL Healthcare Biomagnetic and Nanomaterials Laboratories
 London, United Kingdom

Adeline Hannecart

Department of General, Organic and Biomedical Chemistry
 Laboratory of NMR and Molecular Imaging
 University of Mons
 Mons, Belgium

Gary Hannon

Laboratory for Biological Characterization of Advanced
 Materials (LBCAM)
 Department of Clinical Medicine,
 Trinity Translational Medicine Institute (TTMI)
 Trinity College Dublin
 Dublin, Ireland

Ryan Hilaman

Weinberg Medical Physics, Inc.
 North Bethesda, Maryland

Ingrid Hilger

Department of Experimental Radiology
 Institute of Diagnostic and Interventional Radiology
 University Hospital Jena
 Jena, Germany

Uwe Himmelreich

Biomedical MRI Unit
 Department of Imaging and Pathology
 Faculty of Biomedical Sciences
 Katholieke Universiteit Leuven
 Leuven, Belgium

Ali Kafash Hoshiar

Mechanical and Aerospace Engineering and ReCAPT
 Gyeongsang National University
 Jinju, Gyeongnam, Republic of Korea

and

Industrial and Mechanical Engineering
 Islamic Azad University, Qazvin Branch
 Qazvin, Iran

Kazunori Hoshino

Department of Biomedical Engineering
 University of Connecticut
 Storrs, Connecticut

Yanglong Hou

College of Engineering
 Peking University
 Beijing, China

Sahar Jafari

Weinberg Medical Physics, Inc.
 North Bethesda, Maryland

Yanmin Ju

College of Engineering & College of Life Science
 Peking University
 Beijing, China

Alec P. LaGrow

Department of Physics and Astronomy
University College London
and
UCL Healthcare Biomagnetic and Nanomaterials
Laboratories
London, United Kingdom

Maxime Latulippe

Polytechnique Montréal
Department of Computer and Software Engineering
Institute of Biomedical Engineering
Nanorobotics Laboratory
Montréal, Canada

Sophie Laurent

Department of General, Organic and Biomedical Chemistry
Laboratory of NMR and Molecular Imaging
University of Mons
Mons, Belgium

Tuan Anh Lea

Mechanical and Aerospace Engineering and ReCAPT
Gyeongsang National University
Jinju, Gyeongnam, Republic of Korea

Sim Siong Leong

School of Chemical Engineering
Universiti Sains Malaysia
Nibong Tebal, Penang, Malaysia

Ning Li

Polytechnique Montréal
Department of Computer and Software Engineering
Institute of Biomedical Engineering
Nanorobotics Laboratory
Montréal, Canada

JitKang Lim

School of Chemical Engineering
Universiti Sains Malaysia
Nibong Tebal, Penang, Malaysia

Siew Chun Low

School of Chemical Engineering
Universiti Sains Malaysia
Nibong Tebal, Penang, Malaysia

Shinya Maenosono

School of Materials Science
Japan Advanced Institute of Science and Technology
Nomi, Ishikawa, Japan

Mauro Magnani

Department of Biomolecular Sciences
University of Urbino Carlo Bo
Urbino (PU), Italy

Lamar O. Mair

Weinberg Medical Physics, Inc.
North Bethesda, Maryland

Bella B. Manshian

Biomedical MRI Unit
Department of Imaging and Pathology
Faculty of Biomedical Sciences
Katholieke Universiteit Leuven
Leuven, Belgium

Irena Markovic-Milosevic

Powder Technology Laboratory
Institute of Materials
École Polytechnique Fédérale de Lausanne (EPFL)
Lausanne, Switzerland

Sylvain Martel

Polytechnique Montréal
Department of Computer and Software Engineering
Institute of Biomedical Engineering
Nanorobotics Laboratory
Montréal, Canada

Damien Mertz

Institut de Physique et Chimie des Matériaux de Strasbourg
Centre National de la Recherche Scientifique (CNRS)
Université de Strasbourg
Strasbourg Cedex, France

Mahmood Mohammadi

Polytechnique Montréal
Department of Computer and Software Engineering
Institute of Biomedical Engineering
Nanorobotics Laboratory
Montréal, Canada

Rohimah Mohamud

School of Medical Science
Universiti Sains Malaysia
Kubang Kerian, Kota Bharu, Kelantan, Malaysia

Stéphane Mornet

Institute for Condensed Matter Chemistry of Bordeaux
(ICMCB)
National Center for Scientific Research, CNRS
University of Bordeaux
Pessac, France

María Moros

Istituto di Scienze Applicate e Sistemi Intelligenti 'Eduardo
Caianiello'
Consiglio Nazionale delle Ricerche
Pozzuoli, Italy

Laurence Motte

Laboratory for Vascular Translational Science
Université Paris 13
Sorbonne Paris Cité
Bobigny, France

Robert N. Muller

Department of General, Organic and Biomedical Chemistry
Laboratory of NMR and Molecular Imaging
University of Mons
Mons, Belgium

Aleksandar N. Nacev

Weinberg Medical Physics, Inc.
North Bethesda, Maryland

Jung Kwon (John) Oh

Department of Chemistry and Biochemistry
Concordia University
Montreal, QC, Canada

Yongxin Pan

France-China Bio-Mineralization and Nano-Structures
Laboratory
Palaeomagnetism and Geochronology Laboratory
and
CAS Key Laboratory of Earth and Planetary Physics
Institute of Geology and Geophysics
Chinese Academy of Sciences
Beijing, China

Adriele Prina-Mello

Laboratory for Biological Characterization of Advanced
Materials (LBCAM)
Centre for Research on Adaptive Nanostructures and
Nanodevices (CRANN)
Department of Clinical Medicine
Trinity Translational Medicine Institute (TTMI)
Trinity College Dublin
Dublin, Ireland

Vittoria Raffa

Università di Pisa
Department of Biology
Pisa, Italy

Vincent Russier

Institut de Chimie et des Matériaux Paris-Est-UMR 7182
CNRS and UPEC
Thiais, France

Marie-Louise Saboungi

Institut de Minéralogie, de Physique des Matériaux et de
Cosmochimie Sorbonne Universités
UPMC Univ Paris 06
UMR Museum National d'Histoire Naturelle
IRD UMR 206
Paris, France

Ali Shademani

Department of Biomedical Engineering
University of British Columbia
Vancouver, Canada

Benjamin Shapiro

Fischell Department of Bioengineering
Institute for Systems Research
University of Maryland, College Park
College Park, Maryland

Stefaan J. Soenen

Department of Imaging and Pathology
Faculty of Biomedical Sciences
Katholieke Universiteit Leuven
Leuven, Belgium

Dimitri Stanicki

Department of General, Organic and Biomedical Chemistry
Laboratory of NMR and Molecular Imaging
University of Mons
Mons, Belgium

Pavel Stepanov

Weinberg Medical Physics, Inc.
North Bethesda, Maryland

Grazyna Stepień

Institute of Nanoscience of Aragón
University of Zaragoza
Zaragoza, Spain

Diqing Su

The Center for Micromagnetics and Information
Technologies (MINT)
Department of Chemical Engineering and Material Science
University of Minnesota
Minneapolis, Minnesota

Maryam S. Tabatabaei

Polytechnique Montréal
Department of Computer and Software Engineering
Institute of Biomedical Engineering
Nanorobotics Laboratory
Montréal, Canada

Mari Takahashi

School of Materials Science
Japan Advanced Institute of Science and Technology
Nomi, Ishikawa, Japan

Nguyễn T. K. Thanh

Department of Physics and Astronomy
University College London
and
UCL Healthcare Biomagnetic and Nanomaterials Laboratories
London, United Kingdom

Shiyan Tong

College of Engineering & College of Life Science
Peking University
Beijing, China

Charles Tremblay

Polytechnique Montréal
Department of Computer and Software Engineering
Institute of Biomedical Engineering
Nanorobotics Laboratory
Montréal, Canada

Akif Emre Türelİ

Research and Development Department
MJR PharmJet GmbH
Überherrn, Germany

Nazende Günday Türelİ

Research and Development Department
MJR PharmJet GmbH
Überherrn, Germany

Melissa Anne Tutty

Laboratory for Biological Characterization of Advanced
Materials (LBCAM)
Department of Clinical Medicine
Trinity Translational Medicine Institute (TTMI)
Trinity College Dublin
Dublin, Ireland

Luce Vander Elst

Department of General, Organic and Biomedical Chemistry
Laboratory of NMR and Molecular Imaging
University of Mons
Mons, Belgium

Sabino Veintemillas-Verdaguer

Department of Energy, Environment and Health
Instituto de Ciencia de Materiales de Madrid (ICMM)
Consejo Superior de Investigaciones Científicas, CSIC
Madrid, Spain

Jian-Ping Wang

The Center for Micromagnetics and Information
Technologies (MINT)
Department of Electrical and Computer Engineering
University of Minnesota
Minneapolis, Minnesota

Irving N. Weinberg

Weinberg Medical Physics, Inc.
North Bethesda, Maryland

Kai Wu

The Center for Micromagnetics and Information
Technologies (MINT)
Department of Electrical and Computer Engineering
University of Minnesota
Minneapolis, Minnesota

Swee Pin Yeap

Faculty of Engineering, Technology and Built Environment
UCSI University
Kuala Lumpur, Malaysia

Jungwon Yoon

School of Integrated Technology
Gwangju Institute of Science and Technology
Gwangju, Republic of Korea

Martin Zeltner

Functional Materials Laboratory
Institute for Chemical and Bioengineering
Department of Chemistry and Applied Biosciences
ETH Zurich
Zurich, Switzerland

Hongbin Zhang

Department of Mechanical Engineering
University of British Columbia
Vancouver, Canada

Xingming Zhang

School of Naval Architecture and Ocean Engineering
Harbin Institute of Technology at Weihai
Weihai, Shandong, China



Taylor & Francis

Taylor & Francis Group

<http://taylorandfrancis.com>



Taylor & Francis

Taylor & Francis Group

<http://taylorandfrancis.com>



Taylor & Francis

Taylor & Francis Group

<http://taylorandfrancis.com>

22 Magnetic Nanoparticles for Neural Engineering

Gerardo F. Goya and Vittoria Raffa*

CONTENTS

22.1 Historical Summary and State of the Art.....	395
22.2 Magnetism of Single-Domain Nanoparticles	396
22.2.1 Magnetic Field–Magnetic Nanoparticle Interactions	397
22.2.2 Physical Features of Magnetic Nanoparticles.....	397
22.2.3 Instrumentation: Simulation and Application of Magnetic Forces	398
22.3 Magnetic Actuation on Neural Cells	399
22.3.1 Effects of DC Magnetic Fields on Neural Cells	399
22.3.2 Magnetic Forces Can Actuate on Cells	400
22.4 Nerve Repair.....	401
22.4.1 Magnetic Guidance.....	401
22.4.2 Neuroprotection	402
22.4.3 Magnetofection	402
22.4.4 Magnetotransduction	404
22.4.5 Scavenging Strategies.....	404
22.4.6 Cell Therapies.....	405
22.5 Outlook for the Future	405
Acknowledgements.....	405
References.....	405

22.1 HISTORICAL SUMMARY AND STATE OF THE ART

Nerve damage and neurological pathologies are two problems of significant medical and economic impact because of the hurdles of losing nerve functionality as a consequence of nerve injury or degenerative diseases (ND). Nerve regeneration is a complex biological phenomenon.¹ In the peripheral nervous system (PNS), nerves regenerate spontaneously only when injuries are minor. Short gaps can be repaired directly by mobilization of the proximal and distal stumps with end-to-end coaptation and epineural suturing. Long nerve gaps greater than 2 cm require additional material to bridge the defect. The current repair method is the use of autologous nerve grafts (autografts), which provide the regenerating axons with a natural guidance channel populated with functioning Schwann cells surrounded by their basal lamina.¹ Nerve autografting, however, is far from an optimal treatment, and there is suboptimal functional recovery despite technical excellence. These grafts are taken primarily from the sural nerve of the patient. Surveys of the clinical literature show that approximately half of patients with median and ulnar nerve repairs experience satisfactory motor and sensory recovery.² The main reasons for the poor functional recovery rates associated with

autografts are unavailability of motor nerves (these grafts are primarily sensory) and mismatch in axonal size.³ The use of autograft has also the disadvantages associated to the requirement for a second surgical site (donor site morbidity, donor site mismatch and the possibility of painful neuroma formation and scarring).⁴ The use of nerve guidance conduits (NGCs) is the only clinically approved alternative to the autograft for the treatment of large peripheral nerve injuries. They provide a conduit during the nerve regeneration process for the diffusion of growth factors secreted by the injured nerve ends and to limit the injury site infiltration by scar tissue.⁵ However, commercially available devices, based on biodegradable polymer or collagen-based hollow tubes, do not match the regenerative levels of autografts, providing good performances only for short defects (<2 cm) but poor functional recovery for longer nerve gaps.⁶ Current knowledge suggests combining the use of NGCs with strategies of molecular or cellular therapies. Molecular therapies deals with the delivery of molecules such as guidance cues (netrins, ephrins, semaphorins and other molecules capable of orientating migrating and growing cells) and factors influencing neuronal growth (e.g. growth factors, neurotransmitters, extracellular matrix proteins).⁷ Cell therapies involve cell transplantation to reduce tissue loss, promote axonal regeneration, facilitate myelination of axons or promote the secretion of factors sustaining the regeneration process. The nanotechnology applied to neural development, repair and

* Corresponding author.

protection aspire to implement these approaches for optimal regeneration and recovery of function and to solve those drawbacks arising from the invasiveness of macroscopic implants, including the dependence of the overall performance of such implants to physiological reactions (e.g. fibrosis). Low invasiveness and high selectivity of the growth stimulation are usually conflicting requirements and thus new approaches must be pursued in order to overcome such limitations.

Repairing therapies for those injuries of the central nervous system (CNS) of either the brain or spinal cord are much more challenging. Because the brain coordinates all higher-level functions and communicates with the PNS through the spinal cord, the cellular responses to a mechanical insult and posttrauma situation are numerous, and they are not well understood. Anyhow, once the CNS injury is produced, it initiates a cascade of deleterious events that can affect both cell body and axonal function, resulting in continued dysfunction and prolonged degeneration. For this type of CNS damage, cell therapy is the only therapeutic strategy that proved to work so far. Injured central axons do not spontaneously regenerate. However, the knowledge accumulated during the last two decades challenged the notion that neurons of CNS lack regeneration ability. Although in the 19th century Santiago Ramon y Cajal first suggested the idea that central axons could regenerate but the CNS does not offer a permissive environment, the extended concept of neuroregeneration, including the possibility of neurogenesis and neuroplasticity is a relatively recent one. The notion that neurogenesis is possible led to the idea of implanting viable cells as a therapeutically sound approach in neuroscience. Experimentally, this was demonstrated by transplanting a sciatic nerve explant into optic nerve lesions: the optical nerve regenerated across the graft but growth ceased as soon axons had crossed the graft and reached the interface with the CNS.⁸ It is likely that the regenerative potential of central axons is expressed when the CNS glial environment is changed to that of the PNS.⁹ It was proposed to bypass the problem by transplanting some specific cell type, which could provide a permissive environment for elongated axon growth, similarly to the Schwann cells of peripheral nerves.¹⁰ Thirty years later this hypothesis was tested for the first time in a 38-year-old male with a complete chronic thoracic spinal cord injury (SCI). This patient received an autologous sural nerve graft to bridge an 8-mm gap and the transplantation of glia olfactory ensheathing cells (OECs) in the proximal and distal nerve stumps; he experienced functional regeneration of supraspinal connections.¹¹ Some of clinical studies using cell therapy have been or are being conducted for the treatment of chronic SCI,^{*} traumatic SCI,[†] amyotrophic lateral sclerosis,[‡] Parkinson's Disease,[§] cervical and thoracic SCI,[¶] age-related macular degeneration,^{**} etc.

These are early stage trials (phase I/II) to assess the safety of the treatment, which is essentially unknown despite a large amount of data available from preclinical experimentation.

Nanotechnology comes into neuroscience to provide additional ways to tackle the above-mentioned problems. Since nanoparticles (NPs), and more generally nanostructures, can be made small enough to interact with subcellular structures, the possibilities of intracellular targeting and actuation on damaged neural cells are countless. Inorganic NPs can be engineered as drug carriers alone for releasing neuroregenerative drugs, as reported using hollow silica NPs with porous walls to control the drug release kinetics.¹² Also, different physical properties of the NP's core or coating can be used to trigger the release, providing spatial and temporal control of the dose. The possibility of surface functionalization of NPs adds potential increase of specificity and/or hydrophobicity solutions for already existing therapeutic drugs. Among these strategies, the use of noncontact forces such as magnetic fields provides alternatives for remote NP actuation and activation. This chapter will focus on the new solutions nanotechnology can provide for neurological diseases, through engineered MNPs applied to neuroprotection and neuroregeneration. Also, the application of MNPs as magnetic actuators to position or guide neural cells by an external magnetic field will be described and discussed. In the first part we have included a description of the magnetism related to MNPs, as well as the theoretical framework for magnetic field interactions with biological systems. In the second part of the chapter, we offered an outline of the different strategies based on the use of MNPs and magnetic fields, applied to (a) neuroprotection in neurodegenerative diseases and (b) nerve regeneration following injury. We also describe and discuss those relevant MNP-based strategies successfully employed to remotely guide neuronal growth under the action of magnetic fields.

22.2 MAGNETISM OF SINGLE-DOMAIN NANOPARTICLES

The possibility of remote actuation on a nanoscale object has been understood since long ago as a way to manipulate biological systems.¹³ From the physical point of view, the action-at-a-distance is a consequence of the interaction among any magnetic dipole (the basic entity in magnetostatics) having magnetic moment $\mathbf{m}$ and the magnetic flux density $\mathbf{B}$, also known as magnetic induction.¹⁴ In the general case, the force on a magnetic moment $\mathbf{m}$ exerted under a magnetic induction $\mathbf{B}$ is given by the expression

$$\mathbf{F} = \nabla(\mathbf{m} \cdot \mathbf{B}), \quad (22.1)$$

where the spatial derivative implies that a nonuniform field is required to apply forces. In addition, the $\mathbf{B}$ field exerts a torque $\mathbf{N} = \mathbf{m} \times \mathbf{B}$ on the magnetic moment $\mathbf{m}$ that will align the dipole parallel to $\mathbf{B}$. Therefore, for those applications that require maximizing the magnetic forces between the external field $\mathbf{B}$ and the magnetic moment μ of the MNPs, the usual strategies rely on (a) the design of optimized magnetic field

* www.clinicaltrials.gov. Studies ref. NCT01772810, NCT02688049

† www.clinicaltrials.gov. Study ref. NCT02326662

‡ www.clinicaltrials.gov. Studies refs. NCT01730716, NCT01640067, NCT01348451

§ www.clinicaltrials.gov. Study ref. NCT02452723

¶ www.clinicaltrials.gov. Studies refs. NCT02163876, NCT01321333

** www.clinicaltrials.gov. Study ref. NCT01632527

profiles, and (b) the synthesis of MNPs with large magnetic moments. The former choice is rather old and there is an extensive bibliography on numerical methods and magnetic field configurations.^{15–17} For a comprehensive review of nanomagnetism and magnetic properties of MNPs the reader is referred to the comprehensive work of D. Ortega (Chapter 1: Structure and Magnetism in Magnetic Nanoparticles in the book *Magnetic Nanoparticle: From Fabrication to Clinical Applications*).¹⁸

The choice of the material for the magnetic core of MNPs is related to the physical and magnetic properties of the corresponding bulk phase. However, below a given critical particle diameter $d < d_{\text{crit}}$ (with $30 \leq d_{\text{crit}} \leq 100 \text{ nm}$, depending on the material's nature) the magnetic structure of the particle's core is different than the bulk material in the sense that domain walls collapse into a single magnetic domain. A deeper analysis of the concepts of magnetic domains, magnetic order in small particles and superparamagnetism is beyond the scope of this chapter, and the reader is referred to Ortega¹⁵ and the classic book by B.D. Cullity⁶ (Chapter 8). The value of d_{crit} is determined by the magnetic anisotropy (K) and the exchange stiffness coefficient (A) of the bulk material, and $d < d_{\text{crit}}$ defines a size regime below which the magnetic cores are magnetically ordered in a single direction. Therefore, this spin alignment results in a net magnetic moment of several hundreds of Bohr magnetons (Bohr magneton is the elementary unit of magnetic moment, defined in SI units in terms of the electron charge e , and mass m_e , and the reduced Planck constant $\hbar$, by $\mu_B = e\hbar/2m_e$). The magnetostatic energy of a single-domain MNP (i.e. the magnetic energy in the presence of an externally applied magnetic field) is proportional to its volume V , and this energy competes with the thermal energy to keep the magnetic moment spatially fixed.¹⁶ Around room temperature (i.e. within the 25–45°C range), where most biomedical uses occur, the thermal energy can be of the same order than the magnetostatic energy for small applied fields. Therefore, the thermally induced magnetic relaxation impairs the magnetic alignment of $\mathbf{m}$ and $\mathbf{B}$ diminishing the magnetization at low fields. For MNPs with average size $< 30 \text{ nm}$ thermal relaxation is predominant and thus affects the efficacy of those biomedical applications that require full magnetic saturation at room temperature. For these applications, the design of MNPs must consider average particle size and/or magnetic anisotropy large enough to prevent thermal relaxation.

22.2.1 MAGNETIC FIELD–MAGNETIC NANOPARTICLE INTERACTIONS

The strategy of using MNPs to actuate cells mechanically can be traced back to the year 1920, when W. Seifriz¹⁷ proposed the use of ‘minute particles of magnetic material’ to measure the elasticity of the cell cytoplasm. Since then, a large amount of theoretical and experimental work on magnetically loaded cells has been reported.¹⁸ The physical concept behind this approach is based on the interaction between the magnetic (dipole) moment $\mathbf{m}$ of MNPs and a spatially

inhomogeneous magnetic field $\mathbf{B}$,¹⁹ as described by Equation 22.1. For a spherical MNP composed of magnetite, Fe_3O_4 , with diameter $d = 50 \text{ nm}$, a magnetic moment of $\mathbf{m} \approx 7 \times 10^{-17} \text{ Am}^2$ can be estimated.²⁰ Assuming a commercially available NdFeB magnet (e.g. type N50) of cubic shape with dimensions $1 \times 1 \times 1 \text{ cm}^3$, a single MNP located at a distance of 5 mm from the surface will experience an average force $F \approx 2.1 \times 10^{-15} \text{ N}$. This force is larger than the gravitational force ($\sim 10^{-18} \text{ N}$).²¹ In addition, biomedical applications imply that the MNPs are immersed in a fluid and therefore the Stokes law predicts that any particle moving with velocity $\vec{v}$ will experience a drag force $\vec{F}_D$ given by $\vec{F}_D = 6\pi\eta r\vec{v}$, where η is the viscosity of the medium and r is the radius of the MNP. This force is size-dependent, but for the applications in quasi-stationary conditions such as those existing in a cell culture, the velocity factor makes this force small enough to discard it.²² On the other hand, diffusional forces due to Brownian motion are also size dependent and cannot be neglected in colloidal systems at room temperature. A complete analysis of the influence of Brownian forces of single-domain MNPs under external magnetic field requires the use of stochastic approaches, such as the stochastic Eulerian–Lagrangian method, which is beyond the scope of the present description. Summarizing, to produce a measurable pulling-magnetic force, the MNPs have to be designed to maximize their magnetic moment $\mathbf{m}$ under the $\mathbf{B}$ values applied, and the magnetic field profile must be planned to produce enough field gradients for the experimental conditions required.²³

22.2.2 PHYSICAL FEATURES OF MAGNETIC NANOPARTICLES

Two iron oxides, namely magnetite (Fe_3O_4) and maghemite ($\gamma\text{-Fe}_2\text{O}_3$), are by far the most used materials as a constituent of MNPs in the biomedical field.²⁴ These oxides crystallize in the cubic spinel structure, where two cationic sites with different geometries define the two magnetic sublattices, labelled as A and B sites. The cations at A and B sublattices have different atomic magnetic moments and result in a noncancelling total magnetic moment, and this type of magnetic order is known as ferrimagnetism. The macroscopic behaviour is similar to a ferromagnetic one, with remanence (i.e. a net magnetization at zero applied field), hysteresis (i.e. magnetization dependence on the magnetic history) and magnetic ordering (Néel) temperature. As mentioned before, in MNPs with size below the critical domain size the formation of domain walls is energetically unfavourable and the magnetic state has a single-domain configuration. If the MNP's volume is small enough, the thermal fluctuations at room temperature makes the magnetic moment to relax within timescales shorter than the measuring time, yielding a null-average of the magnetic moment.²⁵ This state is known as superparamagnetism. The magnetic relaxation of MNPs in magnetic colloids is therefore governed by the dynamics of the magnetization vector and have been modelled by Usov et al.²⁶ using the stochastic Landau–Lifshitz model.

As mentioned before, the specific properties of a given magnetic material must be considered when using MNPs as pulling agents. Specifically, those aspects governing the interaction expressed by Equation 22.1 between the magnetic field $\mathbf{B}$ and the magnetic moment $\mathbf{m}$ of the material. Since the material properties of the MNPs enter Equation 22.1 through the magnetic moment $\mathbf{m}$, it is expected that the resulting magnetic forces should be more or less independent on the physicochemical environment of the MNPs for a given application. Instead, the most relevant parameters are the saturation magnetic moment M_s of the particles and their magnetic anisotropy. Together with the average volume V , these parameters will define the magnetic response of the material under the magnetic field intensity H applied. If the MNPs have a single-domain configuration, the magnetic moment measured under a given H value is given by

$$M(T, H) = M_s \mathcal{L}(M_s V H / k_B T), \quad (22.2)$$

where $\mathcal{L}(x)$ is the Langevin function, and $k_B T$ is the thermal energy factor at temperature T . This expression, together with Equation 22.1, show that if the MNPs are small enough the thermal fluctuations will render the magnetization small therefore decreasing the magnetic force. On the other hand, for multidomain MNPs the magnetization is governed mainly by domain wall motion and for large H values also by magnetic moment rotation within domains. Therefore, the preferred materials that provide magnetic saturation at low fields (and therefore large magnetic forces) would be magnetically soft materials (i.e. low magnetic anisotropy) without crystal-line defects or vacancies, to avoid domain wall pinning.

22.2.3 INSTRUMENTATION: SIMULATION AND APPLICATION OF MAGNETIC FORCES

Experimentally, the $\mathbf{B}$ profiles required for *in vitro* experiments can be produced by a suitable configuration of

permanent magnets (e.g. FeSm₅ or NdFeB magnets) as well as different types of electromagnets. In most biomedical applications, processing conditions require working within fluidic phases and in small volumes. These prerequisites combine well with the use of microfluidics as a complementary technique to handle highly stable microflows and to fit the small volumes of liquids like culture media for *in vitro* experiments, where the total volumes can be as small as 10⁻⁹ L. The downscaling of magnetic separators allow to integrate them into more complex systems like detection devices for diagnostics and clinical assays, environmental monitoring, food-contaminant analysis, etc.²⁷⁻²⁹ Also, small sample spaces allow larger field gradients to be applied without the need of large magnetic fields.

On the other hand, for larger working spaces the use of high-power electromagnets seems to be the only workable choice. One of the possible arrangements to combine continuous sorting and large working volumes is schematized in Figure 22.1a, where a superconductor coil of cylindrical symmetry surrounds a ferromagnetic matrix immersed in the flowing medium. Here the external field provides the large intensity of $\mathbf{B}$ inside the tube, whereas the ferromagnetic network provides the local inhomogeneity (i.e. field gradient) to retain the magnetic particles. The scalability of magnetic separation by magnetic forces is technically simple, although the amounts of energy required at industrial scales make it expensive. In any case, the use of high-gradient magnetic fields is being used successfully for treatment of industrial wastewaters and removal of heavy metals.³⁰

At small working volumes (i.e. *in vitro* or small *in vivo* applications) the adequate choice of the $\mathbf{B}$ source will depend on the specific details of the experimental setup, but in most cases commercially available permanent magnets can produce suitable magnetic field gradients of several thousand T/m. A simple quadrupole configuration used for magnetic separation is produced by four permanent magnets placed on the external side of a supporting tube through which the colloid is pumped

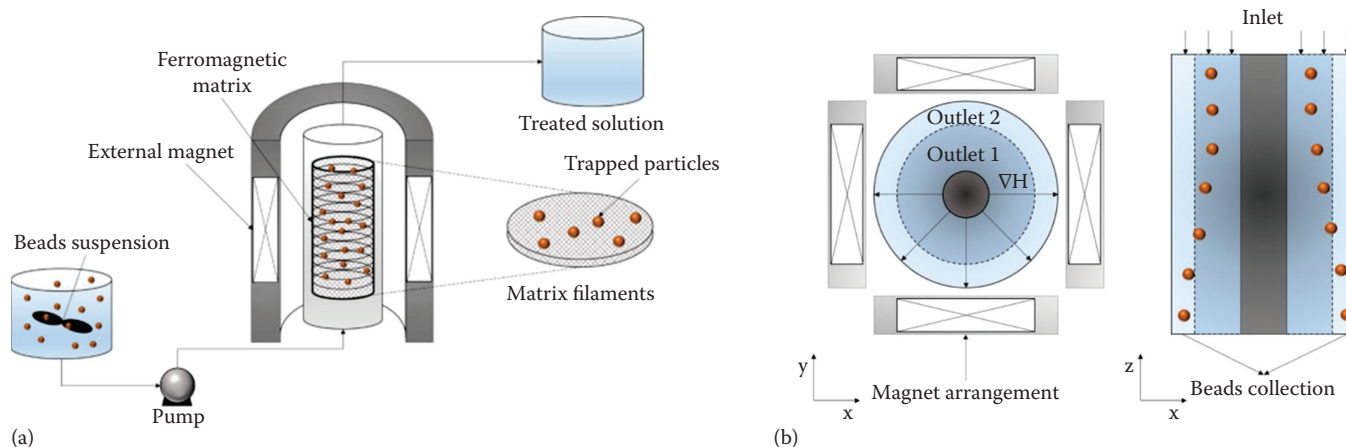


FIGURE 22.1 Schematic drawing of two approaches for magnetic separation under continuous flow sorting (a) a high gradient field separator based on superconducting magnets and (b) a magnetic quadrupole configuration, frequently used in small-volume applications. (Reprinted from *Sep. Purif. Technol.*, 172, J. Gomez-Pastora, X. Z. Xue, I. H. Karampelas, E. Bringas, E. P. Furlani, and I. Ortiz, 16, Copyright 2017, with permission from Elsevier.)

(see Figure 22.1b).³¹ This configuration produces four regions with maximum field along the circular perimeter of the tube, whereas $\mathbf{B} = 0$ at the centre.

A similar approach than the one used for magnetic separation, i.e. the use of the magnetic forces between external dc fields and the MNPs magnetic moment discussed above, is the basis for magnetic applicators designed for magnetic targeting. However, for MNPs to be concentrated at any internal body space there are additional difficulties. First, any realistic *in vivo* situation should consider not only the dynamic nature of the circulating blood but also the nonlinear character of the systemic paths that will carry the MNPs. In addition, the inherent pulling nature of the magnetic forces makes difficult to direct a net magnetic force towards an inner body volume using an external array of magnetic field sources. A potential solution to this problem was proposed through active targeting and accumulation of magnetic actuators to neural cells. This strategy has been successfully applied to control the mammalian nervous system in mice.³²

22.3 MAGNETIC ACTUATION ON NEURAL CELLS

22.3.1 EFFECTS OF DC MAGNETIC FIELDS ON NEURAL CELLS

A substantial portion of the early research on biomagnetism was devoted to elucidating the influence of static and alternate magnetic fields at cellular and tissue levels.³³ Such investigations have disclosed many biochemical pathways that are influenced by a magnetic field. Only a small number of those investigations were related to physiological mechanisms in vertebrates under the influence of static magnetic fields, describing how reactions to magnetic stimuli were effected through the CNS.³⁴ The physical mechanism by which an exogenous magnetic field affects the biological pathways in eukaryotic cells is still under discussion, although there is long-standing experimental evidence that demonstrates the measurable effects on cell proliferation, migration and adhesion.³⁵ The existence of the earth's magnetic field ($H = 39.8$ A/m or 500 mG) provides examples of biological interactions that are well documented in bees, pigeons, bacteria and fish. The phenomena involving the capacity of a living organism to perceive or detect such weak magnetic field is known as magnetoreception.³⁶

Also, the effects of intense static magnetic fields (i.e. up to several MA/m, or kGauss) have been studied in several different animal species, with different results, a relation between long-term application of strong static fields and biological pathways has been suggested. For example, experiments in young mice subjected to strong DC magnetic fields (i.e. $H = 334$ kA/m or 4200 G) have demonstrated measurable effects including growth retardation, changes in the population of bone marrow-derived monocytes, and increased rates of appearance of spontaneous cancer.^{37,38}

As mentioned above, there is abundant experimental evidence that the application of static (or very low-frequency)

magnetic fields on eukaryotic cells affects many biochemical pathways significantly, including cell proliferation, adhesion³⁵ and expression of heat-shock protein.³⁹ In the case of neural cells, the influence of magnetic fields could be expected on those mechanisms involving the exchange of ions through the cell membrane. Theoretical explanations⁴⁰ for these effects were proposed through perturbation effects of the magnetic field on moving charges. Since these neural communication mechanisms involve electrical signaling through ion channels at the cell membrane, it seems reasonable to expect that magnetic fields can influence the dynamics of cross-membrane ion pumping, impacting on cell differentiation and cell growth. However, there is experimental evidence excluding measurable effects on Na⁺ and K⁺ transmembrane currents down to one part in 1000.⁴⁶ On the other hand, it has been suggested that changes in nerve activity when exposed to strong DC magnetic fields (e.g. >100 kA/m) could be related to the diamagnetic anisotropy of some molecular components of the cell membrane. Under high magnetic fields, it is expected that the anisotropy axis of the membrane molecules will align along the field direction, and this realignment would suffice to modify the ion channel activity.

It is interesting to note that the two mechanisms differ on their physical basis: the action of $\vec{B}$ on moving charges $\pm q$ is the Lorentz force $\vec{F} = \pm q(\vec{v} \times \vec{B})$ applied to those charges with velocity $\vec{v}$, whereas the diamagnetic alignment of membrane molecules is the response of the closed-shell orbital atomic moments to the applied magnetic field. These differences make it in principle possible to design experiments to identify which mechanism will contribute under specific conditions. Both effects could be significant under strong fields, but the different B-thresholds at which these mechanisms start to operate and to what extent they are independent remain to be elucidated. In any case, the experimental evidence supporting the influence of static magnetic fields on neural cells is already quite solid, and explains why most reports on clinical effects of magnetic fields refer to the nervous system.⁴⁷

Due to the complex interaction between electric and magnetic phenomena, the disentanglement of each source when a given (electrical or magnetic) experiment is performed is always challenging. The classification of 'pure' magnetic or electrical stimulation can be useful sometimes but the electromagnetic theory makes this distinction unfitting in the sense that a 'pure' static field B can modify the distribution of electrical charges existing in any material. Regarding biological materials (e.g. membranes, tissues, body fluids) it has been shown that the most influential physical parameters to be considered to affect cell functions are the electric and magnetic field amplitudes (E_0 and H_0 , respectively), the intensity of induced currents, the induced voltage and the frequency.⁴³ In any case, general considerations indicate that the time scale of the electromagnetic stimulus must be of the same order of magnitude than the physical mechanism involved because otherwise the time average of the shorter magnetic pulses on the much larger time scales of biochemical dynamics in a cell membrane would produce a null effect out by simple time averaging any effect. For this reason both DC and extremely

low-frequency magnetic fields are the usually chosen regimes to influence the response of biological systems.

Some works published in the 1980s about a 'cyclotron resonant effect' attempted to link weak electromagnetic fields to an enhanced Ca^{2+} transport through cell membrane due to resonant mechanisms.⁴⁴ However, attempts to replicate this effect were unsuccessful.⁴⁵ Moreover, theoretical considerations about the influence of viscosity and molecular collisions in fluid biological media seem to preclude any possibility of resonance associated with ion trajectories in such magnetic fields.

Iron is a relatively abundant element in most living organisms. Therefore, it is not surprising that biomineralization of iron, i.e. the biochemical processes through which an organism synthesizes hard minerals have made magnetite (Fe_3O_4) ubiquitous across both kingdoms of prokaryotes and eukaryotes including bacteria, protozoa and mammals. The occurrence of Fe_3O_4 crystals in the human brain resulting from iron biomineralization was first reported by Kirschvink,⁴⁶ who showed the presence of 20–50 nm crystals both isolated and forming linear structures similar to those typical of magnetotactic bacteria. The presence of nanostructured magnetite in the brain has been related to NDs in which disruption of normal iron homeostasis occurs.⁴⁷ The excess of iron and senile plaques found in brain tissue seem to support this idea.⁴⁸ It is interesting to mention that a recent study has suggested airborne pollution as an exogenous source of the Fe_3O_4 NPs found in brain tissue,⁴⁹ which poses the question of whether the major sources of MNPs in the brain have an internal or external origin. In any case, the idea that these magnetite MNPs within the brain could have relation with some of the biological effects related to AC magnetic fields in humans⁵⁰ merits further investigation.

22.3.2 MAGNETIC FORCES CAN ACTUATE ON CELLS

Although magnetic fields do have an influence on neural tissue, it is evident from the previous discussion that the nature of the interaction makes difficult to envisage their uses for remote tethering or actuation. Magnetic actuation is the action of influencing the behaviour of a cell by magnetic forces, generated from MNPs previously uploaded/attached to the cell.

To have the capacity of influencing axonal growth, magnetic forces must produce an effect larger than the drag forces within the cell, even at the nanometric scale. Magnetic forces originate in the interaction between the magnetic moment of MNPs and the magnetic field, as already discussed in Section 22.2.1, together with drag forces. For cell actuation a way to overcome the effects of drag forces is through the design of the MNPs. Furthermore, novel therapies that use exogenous cells (cell therapy) to gain lost functionalities in target tissues or organs have been proposed, which provide a fascinating tool for concurrent uses for MNPs. For example, stem cell-based treatments have been established as a clinical standard of care for some conditions, such as hematopoietic stem cell transplants for leukaemia and epithelial stem cell-based treatments.⁵¹ Although the scope of potential cell-based

therapies has expanded in recent years due to advances in basic research, attempts to develop a cell-based intervention into an accepted standard of medical practice are particularly difficult processes for different reasons. One of the unresolved issues relating to the clinical use of transplanted cells concerns the localization of these cells to the diseased site, since only a small percentage of the implanted/injected cells *in vivo* reach the desired location.⁵²

There is enough evidence that for neural or neural precursor cells MNPs can be incorporated into the cytoplasm in large amounts. For example, the iron uptake in the oligodendroglial cell line OLN-93 has been reported⁵³ to increase the contents of intracellular iron up to ≈ 200 times the basal concentration in a concentration-dependent way. A comparative study on internalization in primary and immortalized cells showed that immortalized PC12 cells have a more intense activity than primary cells regarding MNP uptake.⁵⁴ The same study revealed that in a mixed (neuronal and glial) primary cell culture the predominant uptake of MNPs was done by microglia, whereas the number of astroglia and oligodendroglia incorporating MNPs was lower. Moreover, comparison against organotypic cocultures of spinal cord and peripheral nerve grafts yielded MNP-uptake levels similar to those of the primary cell cultures.⁵⁴

The way by which a MNP is delivered to the cytoplasmic space can be very different depending on the type of cells or MNPs involved. Little work has been reported on the mechanisms of MNP uptake by neural cells and, more generally, about the interactions between MNPs and neural cell lines. Tay et al. reported a meticulous study on the interactions of MNPs with primary cortical neural networks in different developmental stages.⁵⁵ These authors found that chitosan-coated MNPs were internalized whereas starch-coated MNPs were not, the latter being attached to the cell membrane. By inhibiting selectively different uptake mechanisms, they concluded that the mechanisms by which chitosan-coated MNPs were incorporated was micropinocytosis and clathrin-mediated endocytosis.

The latest evolution of nanoscience into the neuroscience field has provided incipient solutions for the remote guidance of functional cells related to the above-mentioned cell therapies.^{56,57} The ability to introduce MNPs into cells and magnetize them was the first step towards remote manipulation by magnetic fields to carry healing cells to the desired site, enabling the cells to colonize and differentiate into any desired cell type.⁵⁸ Also, different approaches based on magnetic forces to destroy target (cancer) cells have been reported. For example, Kim et al.⁵⁹ have succeeded in provoking cell damage using magnetic microdisks that could be forced to rotate by an external magnetic field of very low frequency (i.e. a few hertz) due to their vortex structure. The mechanical rotation was reported to compromise the integrity of the cell membrane, triggering an apoptotic mechanism. More recently, the same concept has been successfully applied *in vivo* to reduce an intracranial glioma tumour with no observed side effects.⁶⁰

However, the rationale for remote guiding of axonal growth includes not only the successful uptake of the MNPs by the

target cells. Given the large number of cells that participate in the repair after nerve injury, there is the question of whether some specific cell types could be more efficient in internalizing the MNPs injected than the target neurons. Most of the previous reports about the effects of NPs on neural cells (e.g. cell uptake, toxicity, etc.) have been conducted on immortalized cell lines (see for example Riggio et al.⁶¹) and only a few studies have been performed to investigate the effects of MNPs on primary cells of the nervous systems.^{61,62}

The design of any magnetically guided axon regeneration therapy must consider how the external magnetic forces will act on an MNPs-loaded cell. The basis of the remotely guided neural regeneration involves (a) physical mechanisms to direct axonal regrowth along selected directions, and (b) biochemical mechanisms to stimulate axonal elongation across the nerve lesion site.⁶³ Also, the molecular guidance of axonal growth based on high-affinity molecules (such as growth factors and extracellular matrix proteins) can orientate growing cells,⁶⁴ although no therapeutic outcome has yet been reported.

Regarding physical guidance, autologous and heterologous tissue grafts or bioderived materials as scaffolds have been partially successful in providing growth conduits to guide the nerve during regeneration.^{65,66} On the other hand, the uses of contactless magnetic forces have been much less studied. Some studies have been reported to be effective in both axon orientation and growth,⁶⁷ although these results are up to now limited to *in vitro* experiments. For *in vitro* situations, there are specific adhesion forces chemically sticking the cells to a substrate,⁶⁸ and therefore interaction of MNPs with H must be strong enough to overcome the adhesive forces, which have been reported to be in the 1–200 pN range depending on the measuring conditions.⁶⁹

22.4 NERVE REPAIR

22.4.1 MAGNETIC GUIDANCE

The concept of magnetically assisted nerve repair is based on two complementary actions that can be performed when MNPs are used. The first action is related to the interactions with a remote magnetic field, which generates a pulling force from the MNPs to the growing axons. The second, i.e. the possibility of having neurotrophic factors on the MNP's surface, would make it possible to stimulate growth rates during the application. This synergistic approach for nerve repair using MNPs is schematically illustrated in Figure 22.2. It is evident that the complexity of the actual biological process, which includes a plethora of different cell types acting on the injured nerve, makes it necessary to verify some hypotheses regarding the effects and fate of MNPs once they are injected into the injured tissue. For example, Schwann cells are recognized as helpful agents promoting axonal regeneration in the PNS while astrocytes and oligodendrocytes in the CNS are not. Therefore, the successful delivery of MNPs to the target axon will depend on the relative affinity of these cell types for the MNPs.

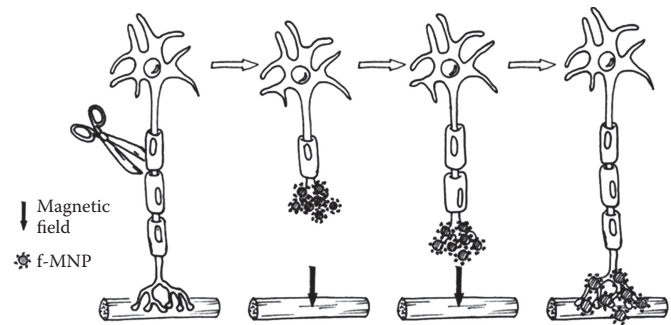


FIGURE 22.2 Schematic illustration of magnetically assisted nerve repair process. The injured nerve is targeted by the magnetic NPs, and then a remote magnetic field guides axonal growth along the field lines. The particles, in turn, could be surface-functionalized with growth-stimulating molecules to accelerate the healing.⁷⁶ (Reprinted from *Nanomed-Nanotechnol.*, 10, C. Riggio et al., 1549, Copyright 2014, with permission from Elsevier.)

Although mechanisms involved in axonal growth are not completely understood, there is increasing evidence that mechanical force generation is a crucial process for both axonal guidance and lengthening.⁷⁰ The existing literature suggests that neurons and their axons possess fine sensors to sense and transduce mechanical force in axon initiation/elongation/guidance. The involvement of mechanical tension in the morphogenesis of the nervous system was clear in the late 1970s when pioneering experimental work revealed that neuronal processes *in vitro* are under tension.⁶⁶ Later, different teams demonstrated that the external application of mechanical tension alone is sufficient to initiate *de novo* axonal sprouting. There is a consensus that neurite elongation is a linear function of the applied force and its rate has been found to be similar to both PNS and CNS (about 0.1–1 $\mu\text{m h}^{-1}$ per pN of applied force). MNPs, which develop a strong magnetic force when an external magnetic field is applied, could be used to induce an extremely rapid regeneration of the injured axons, purely directed by mechanical forces on MNP-labelled axon tracts. Fass and colleagues used magnetic beads to precisely develop forces in the piconewton range, finding cells able to sustain mechanical-driven elongation with applied tensions between 15 and 100 pN.⁷¹ In addition to the evidence that mechanical tension can induce elongation of neurite or process initiation, recently its influence on axonal guidance has also been investigated. It was demonstrated in a neuron-like cell line that MNPs can be used to gain control of directional movements of neurites. Specifically, by using magnetic nanobeads, it was found that the application of 0.5 pN force on cell neurites was enough to preferentially align them along the direction imposed by the mechanical force.⁷ Moreover, using a model based on the effects of the applied forces acting on the receptor–ligand bond, dynamic process of bond loading, breaking and formation during cytoskeletal movements, the authors could reproduce the experimental data successfully.⁶³ A basic setup for this experimental approach using four parallel NdFeB magnets is depicted in Figure 22.3, where the micrograph (inset) shows the preferential growth along the

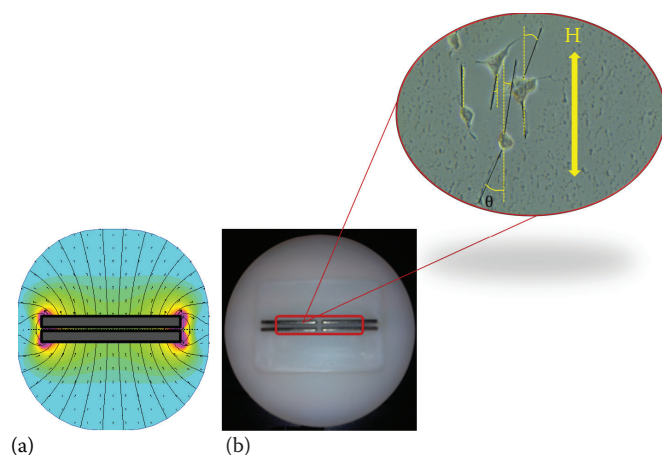


FIGURE 22.3 (a) Representation of the magnetic field applied to the neural PC12 cell cultures. The magnetic field was homogeneous in the Y and X direction (0.19–0.20 T). The maximum magnetic field gradient was 0.019 T/m. (b) Image of the support where the T-25 flasks were incorporated and an example of the images obtained by an optical microscope in the area where the cells are analyzed. The image shows the analysis of the neurite direction; each neurite is manually traced and then the angle formed between the neurite and the direction of the magnetic field (θ) is recorded.

field lines (yellow arrow), quantified through the angle θ between H and the direction of the main dendrites.

The ability to generate mechanical tensions on neurites, to promote elongation, and to guide directional movement could make MNPs a powerful strategy to address the dream of axonal re-innervation from the CNS to the desired target, e.g. the neuromuscular junction. The MNP-mediated mechanical force has also been used to manipulate neuronal compartments. MNPs have been used to bind filopodia cell membrane of retinal ganglion cell growth cone and to elicit axonal growth and guidance by exerting mechanical tension with an externally applied magnetic field.⁷² MNPs functionalized with TrkB agonist antibodies have been used to target the particles to signaling endosomes, to manipulate them by focal magnetic fields, and to alter their localization in the growth cone, thus deregulating growth cones motility and neurite growth.⁷³ The synaptosomes of brain nerve terminal labelled with MNPs were spatially manipulated with external magnetic field without affecting the key characteristics of glutamatergic neurotransmission.⁷⁴ Recently, manipulation via MNP has also been performed at the molecular level, by influencing protein segregation during axonal development, *in vitro* and *in vivo*, to dictate axon formation.⁷⁵ In general, MNPs offer the distinct advantage of being easily functionalized with ligands for high affinity binding to specific neuronal cell types, compartments or proteins,⁷⁶ which makes particularly effective present and future strategies of neuronal manipulation via MNP-induced mechanical forces. MNPs have been used also to manipulate the extracellular environment, which plays a key role in the process of nerve regeneration. Recently, magnetic particles have been used to orientate

collagen fibres under an external magnetic field, opening the possibility to develop oriented scaffolds to strongly promote the process of functional reinnervation.⁷⁷

22.4.2 NEUROPROTECTION

Functionalization of MNPs with neurotrophic factors to promote neuron survival/growth can also be achieved.⁷⁸ Although the free growth factors have a very short half-life (e.g. few minutes)⁷⁹ *in vitro* studies have proved that the conjugation to iron oxide NPs can prolong the biological activity of NGF, glial cell-derived neurotrophic factor (GDNF) and basic fibroblast growth factor (FGF-2).^{79,80} An additional advantage of MNPs is that they can be remotely guided by magnetic forces. They have also been used as magnetically guided nanocarriers for spatially controlled drug delivery, e.g. for local release of anaesthetics for local nerve block⁸¹ or for targeting neurotrophic factors to the blood–brain barrier (BBB).⁸² The idea of improving neuroprotection using drug-loaded nanocarriers through the BBB is many years old.⁸³ The capability of a nanometre-sized device with a therapeutic payload to cross the BBB is appealing since about 95% of the therapeutic drugs for treating CNS diseases fail to do so in the brain.⁸⁴ This is mainly related to the impenetrability of the BBB for such molecules. Several strategies to overcome this problems using MNPs have been reported, based on the functionalization of the particles with peptides, proteins and similar small molecules.⁸²

However, the actual neurotoxicity levels of MNPs *in vivo* are not yet completely known. It has been reported that MNPs entering into the body fluid system can result in adverse effects on the CNS.⁸⁵ Also, systemic administration of MNPs has been reported to induce breakdown of the BBB, an effect not only exclusive of magnetic particles but NPs in general.⁸⁶ Different interactions between MNPs and CNS in physiological vs. pathological conditions cannot be also excluded. A recent work showed that NPs can target myeloid cells in epileptogenic brain tissue, suggesting their use for detecting immune system involvement in epilepsy or for localization of epileptic foci.⁸⁷ A related, more subtle question of whether MNPs influences the physiological brain responses under pathological conditions has been addressed only rarely in the literature, but is certainly a subject that merits investigation.

22.4.3 MAGNETOFECTION

The concept of transfection can be defined as the procedure by which any type of genetic material from a foreign source is introduced into a different mammalian cell. When dealing with DNA, this process enables the expression of proteins from the original source by the host cell's machinery. The transfer of the genetic material can be done by different methods, in many cases using coadjuvant molecules to improve the transfection rates. One example is the use of cationic lipids (e.g. Lipofectamine®) with a positively charged head group that favours DNA condensation and also facilitates the fusion

of the liposome/nucleic acid with the cell membrane prior to the endocytosis.⁸⁸

The first experiments on the use of magnetic fields to enhance nucleic material delivery were reported by C. Mah et al.,⁸⁹ and soon after the term ‘magnetofection’ was coined by C. Plank’s group.⁹⁰ Since then, this concept of MNP-mediated transfection has been customized and improved regarding the dose–response ratios and transfection

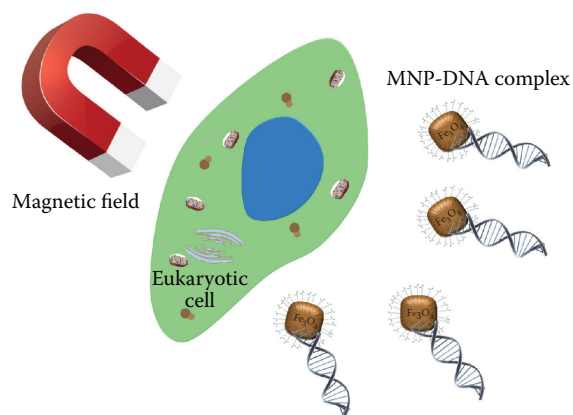


FIGURE 22.4 Schematic illustration of the magnetofection principle. The nucleic acid and the magnetic NP form the magnetic nanovector complex that is pulled towards the cell by a noncontact magnetic force from an external magnetic field gradient. The forces increase the rate of contact events between the vectors and the cell membrane, thus improving the uptake dynamics of the cell.

rates. Today, there are many commercially available kits that provide user-ready MNPs and reagents for routine laboratory applications such as CombiMag™ (Ozbiosciences SAS, France) or Magnetofection™ (Chemicell GmbH, Germany). The basic mechanism is depicted in Figure 22.4: through the use of an external magnetic field gradient, the forces acting on the magnetic vectors increase the contact time of the genetic material and the cell membrane, increasing the uptake dynamics of the cell membrane and thus the efficiency of nucleic acid delivery. Some simple physical models have been proposed for this interaction, based on a drift-diffusion equation through the cell membrane,⁹¹ but a complete model accounting for the different physiological pathways is still lacking. However, there is an emerging consensus that for these applications the surface chemical composition of the MNPs is a key factor determining the final efficiency, irrespective of the details of the magnetic structure of the magnetic cores.

Recently, a method to increase transfection in neural stem cells (NSCs) using MNPs and very low frequency (4 Hz) magnetic fields demonstrated that transfection efficacy could be improved significantly, while keeping the differentiation capabilities unaffected.⁹² As shown from the differentiation profiles in Figure 22.5, magnetofected NSCs show positive for all transfected markers. Moreover, the authors reported that magnetofected NSCs displayed disrupted cell membranes as compared to control cells. Although the physical mechanisms involved are not completely understood, experimental data suggest that the higher efficiency under magnetic fields is due

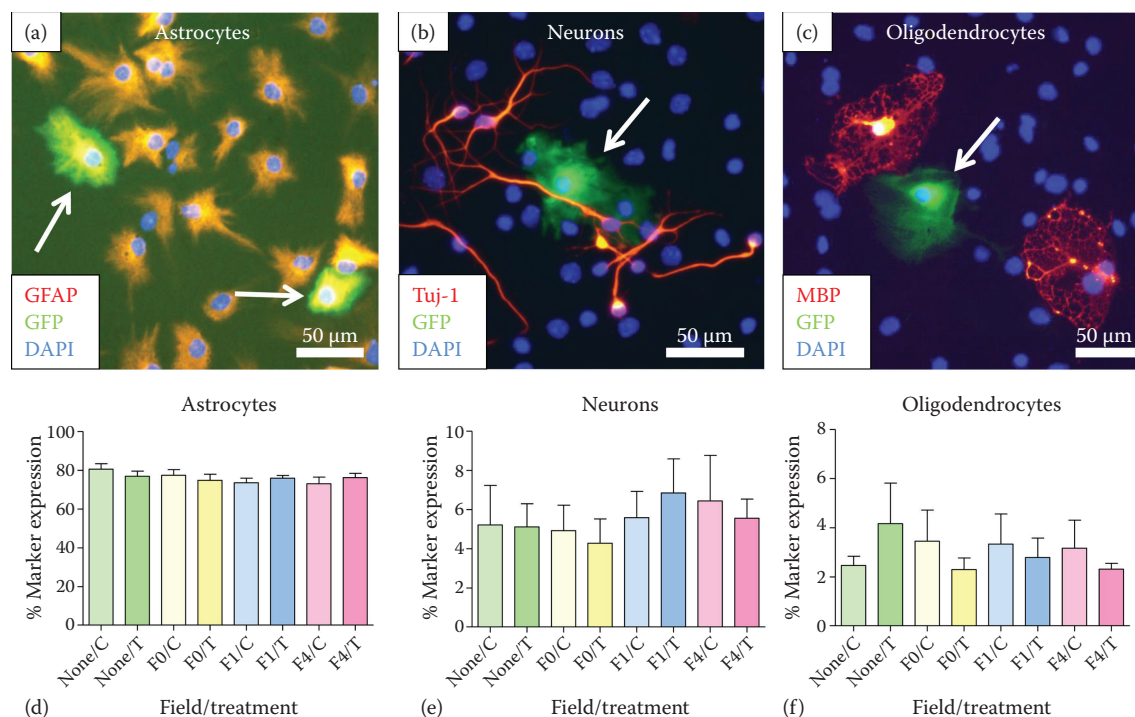


FIGURE 22.5 Triple merged images of magnetofected ($f = 4$ Hz) neural stem cells (NSCs), postdifferentiation showing cells positive for GFAP (a), Tuj-1 (b), and MBP (c). GFP expressing GFAP+ cells are seen in (a, arrows) and GFP+ cells with the morphological appearance of astrocytes in (b and c, arrows). (d–f) Bar charts showing proportions of GFAP, Tuj-1, and MBP positive cells, $n = 4$ cultures. None: no field, F(N): frequency of oscillation, C: control, T: transfected. (Reprinted from *Nanomedicine: Nanotechnology, Biology and Medicine*, 9, C. F., Adams, M. R., Pickard, and D. M., Chari, 737, Copyright 2013, with permission from Elsevier.)

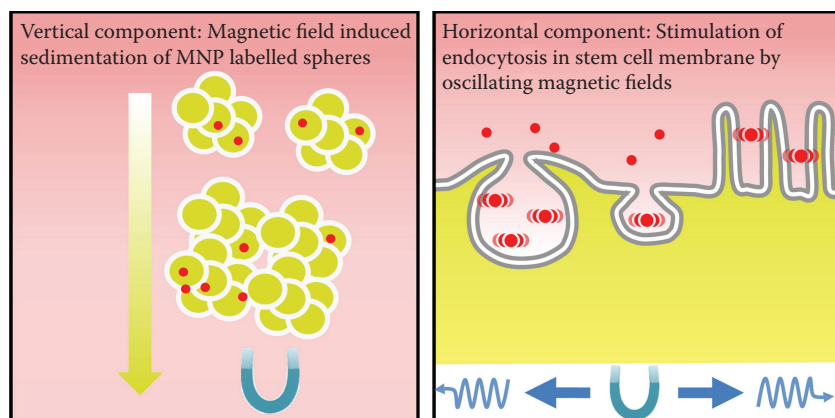


FIGURE 22.6 Proposed mechanism of transfection of neurospheres. Schematic diagram illustrating a hypothetical model to explain the mechanism of oscillating field enhancement of transfection in neurospheres.¹¹⁰ (Reprinted from *Nanomedicine: Nanotechnology, Biology and Medicine*, 9, C. F., Adams, M. R., Pickard, and D. M., Chari, 737, Copyright 2013, with permission from Elsevier.)

to both an increase of the MNP-cell interaction time and a frequency-driven stimulus of the endocytic activity of the cell membrane, as depicted in Figure 22.6.⁹²

22.4.4 MAGNETOTRANSDUCTION

Similarly to the use of magnetic forces, the use of viral vectors has provided a fruitful solution to increase the low efficiency of nonviral gene vectors, a technique known as transduction. The term was coined more than 50 years ago by Zinder et al.,⁹³ in their genetic studies on *Salmonella typhimurium* and has been improved notably along the last decade.⁹⁴ Viral vectors have been intensively used as a tool for fighting NDs, through the delivery of neurotrophic factors that prevent degeneration and enhance recovery of target neurons. The potential of this technique for clinical uses is apparent, especially in the field of NDs. For example, two powerful neuroprotective molecules for the treatment of neurodegenerative pathologies affecting both motor and cognitive functions are GDNF and insulin-like growth factor I (IGF-I).⁹⁵ In spite of some promising results, the efficiency of viral (and nonviral) vectors for therapeutic gene delivery into the brain still remains one of the limiting factors to be overcome before clinical trials can be safely implemented. Additionally, most protocols currently in use for nucleic acid delivery⁹⁶ require some improvement of either the efficiency or specificity of nucleic acid delivery.⁹⁷

Based on the concepts of magnetofection, i.e. the use of magnetic forces on MNPs to improve transfection efficiency, therapeutic approaches against NDs have begun to use magnetically labelled viral units to deliver genetic material. The construction of magnetic viral vectors (usually adenovirus or lentivirus) for a magnetic field-assisted viral transduction has been reported for some years now. This technique is known as *magnetotransduction*, and is often related (but not restricted) to strategies for delivering neuroprotective molecules to target cells as a therapy against ND diseases. One of the main goals of this approach is related to the enhancement in the levels of neurotrophic factors delivered, since it is accepted that an increase in the delivered concentration of

these factors can prevent neural degeneration and enhance recovery of remaining neuron neuroprotective molecules at the target site.⁹⁸

In magnetotransduction, the MNPs also work as the ‘pulling’ agents when conjugated with viral vectors to construct a magnetic-viral vector of higher efficacy than virus or MNPs alone. Some configurations using Fe₃O₄-based MNPs and recombinant adenoviral vector harbouring reporter genes have been already used to magneto-transduce glial and neuronal brain cells (ependymal, hypothalamic and substantia nigra) with high efficiency.⁹⁹ Some proof-of-principle experiments with MNP-AAV (adeno-associated viral) vectors showed partial success,¹⁰⁰ but the need for further optimization of vector formulation remains, especially if neuroprotective and neurotrophic factors (e.g. IGF-1, GDNF) are to be used for clinical applications to ND diseases. If successful, this approach could represent a major improvement towards new therapies for NDs.

22.4.5 SCAVENGING STRATEGIES

When the CNS is affected, nerve injury results in a disruption of the blood–spinal cord barrier. Moreover, the damage induced in surrounding blood vessels stimulates a proliferation of Schwann cells, leucocytes, monocytes and macrophages around the nerve lesion that provokes the loss of nervous tissue. At the cellular level, axons show deteriorated myelin layers, and the resulting growth-inhibitory myelin debris is only partially removed by macrophages. Therefore, a containment/scavenging protocol is desired before actual nerve regeneration. Gathering those cells that are activated in response to pathological situations can be achieved by the use of remote magnetic forces on the injured area. The incorporation of MNPs by scavenger cells has been already observed in organotypic culture,⁶¹ and therefore it can be expected that similar targeting can be achieved *in vivo*.¹⁰¹ Indeed, the *in vitro* preloading of macrophages and the subsequent infiltration *in vivo* for magnetic resonance imaging of injured nerve has been successfully tested some years ago.¹⁰² It is, therefore,

a matter of time before similar magnetic labeling of scavenger cells can be used for improved magnetically driven nerve repair. MNPs possess themselves scavenging properties. In particular, their capacity to scavenge free radicals has been used to attenuate oxidative damage induced by H_2O_2 in SCI rats when localized by an external magnetic field.¹⁰¹ Additionally, their functionalization with biomolecules can confer new scavenger capabilities, as recently demonstrated by MNP functionalization with O-methyl- β -cyclodextrin to reduce the extracellular level of L-glutamate in brain nerve terminals.¹⁰³

22.4.6 CELL THERAPIES

Cellular therapies exploit the regenerative potential of cells for nerve repair.¹⁰⁴ They are considered promising, especially for the repair of CNS injuries and long gaps in the PNS. Several cell types such as stem cells, Schwann cells, OECs have been utilized as transplantable cells in nerve regeneration, demonstrating improved regenerative outcomes^{105,106} but, similarly to any cell-based strategy, this approach suffers from drawbacks, which limit the translation from experimental to clinical stages. A great help for implementing safe and effective cell transplantation could be the development of strategies for cell homing and cell tracking, allowing for monitoring of the fate of the transplanted cells and to retain them in the injury/pathology site, maximizing the therapeutic effects while avoiding dangerous migrations to ectopic sites. Several lines of evidence suggest that MNPs hold a great potential to overcome these limitations. Recently, a clinical study* has demonstrated in healthy volunteers that MNP can be used for *in vivo* tracking of magnetically labelled human mononuclear cells using MRI scanning. Following intravenous administration, the distribution of iron-labelled cells was monitored as well as their ability to migrate to a site of inflammation. Cell labeling with MNPs can be thus easily imaged via MRI and this approach offers the distinct advantage to correlate the study outcome to the cell localization at the site, or biodistribution in the organism. MNPs have been used to label oligodendrocyte precursor cells, which showed high promise as a transplant population to remyelinate nerve fibres and promote regeneration in the CNS. Indeed, clinical trials using these types of cells have been initiated in some areas.¹⁰⁷ The migration of MNP labelled OPCs was followed via MRI, when injected into the spinal cord of myelin-deficient rats¹⁰⁸ or after transplantation into adult rat brain.¹⁰⁹ Magnetic manipulation is also an advantageous method for guiding cells remotely. Neural progenitor cells¹¹⁰ or olfactory ensheathing cells¹¹¹ have been labelled with MNPs and magnetically localized to promote axon growth in organotypic cocultures. This approach was also used *in vivo* to remotely guide MNP labelled stem cell in the spinal cord of SCI mice, demonstrating enhanced localization and axon regeneration.

22.5 OUTLOOK FOR THE FUTURE

There are several nanotherapies already proposed as substitutes for (a) surgical nerve grafting after peripheral nerve injury, (b) pharmacological treatment after drug abuses and (c) neuroprotective drug delivery.^{112–114} However, there are no reports to date that can show conclusive clinical improvements over the established surgical procedures. The near future will probably see new nanotherapies as adjuvant protocols. MNPs have already opened new paths for noninvasive therapies based on the exploitation of the remotely driven mechanical forces on MNP-loaded neurons. The ability of these approaches to promote migration and axonal elongation/growth have already passed the first proof-of-concept challenges, but many fundamental questions are yet unresolved. It is also clear that a 'second generation' of enhanced MNPs is required offering minimum toxicity and better reproducibility. A major issue still not addressed, which will determine the final efficacy of these magnetic vectors, is the creation of a flexible surface for functionalization with neurotrophic/neuroprotective factors. If this flexible platform is developed, it will open boundless possibilities for novel molecular therapies, as well as the basis (together with multipotent stromal cells) for more effective cell therapies.

ACKNOWLEDGEMENTS

This work was partially supported by the Spanish Ministerio de Economía y Competitividad (MINECO) through project MAT2016-78201-P; and the Aragon Regional Government (DGA, Project No. E26) and the Wings for Life Spinal Cord Research Foundation (WFL, Project No. 163).

REFERENCES

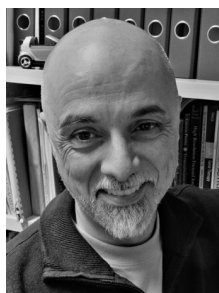
1. Millesi H. 2007. Bridging defects: Autologous nerve grafts. *Acta Neurochirurg. Suppl.* **100**, 37–8.
2. Ruijs A C, Jaquet J B, Kalmijn S, Giele H and Hovius S E. 2005. Median and ulnar nerve injuries: a meta-analysis of predictors of motor and sensory recovery after modern microsurgical nerve repair. *Plastic Reconstruct. Surg.* **116**, 484–94; discussion 95–6.
3. Lin M Y, Manzano G and Gupta R. 2013. Nerve allografts and conduits in peripheral nerve repair. *Hand Clin.* **29**, 331–48.
4. Deumens R, Bozkurt A, Meek M F, Marcus M A, Joosten E A, Weis J and Brook G A. 2010. Repairing injured peripheral nerves: Bridging the gap. *Progr. Neurobiol.* **92**, 245–76.
5. Daly W, Yao L, Zeugolis D, Windebank A and Pandit A. 2012. A biomaterials approach to peripheral nerve regeneration: bridging the peripheral nerve gap and enhancing functional recovery. *J. R. Soc. Interface/R. Soc.* **9**, 202–21.
6. Pabari A, Lloyd-Hughes H, Seifalian A M and Mosahebi A. 2014. Nerve conduits for peripheral nerve surgery. *Plastic Reconstruct. Surg.* **133**, 1420–30.
7. Piotrowicz A and Shoichet M S. 2006. Nerve guidance channels as drug delivery vehicles. *Biomaterials.* **27**, 2018–27.
8. Villegas-Perez M P, Vidal-Sanz M, Bray G M and Aguayo A J. 1988. Influences of peripheral nerve grafts on the survival and regrowth of axotomized retinal ganglion cells in adult rats. *J. Neurosci.* **8**, 265–80.

* www.clinicaltrials.gov. Study ref. NCT01169935

9. David S and Aguayo A J. 1981. Axonal elongation into peripheral nervous system “bridges” after central nervous system injury in adult rats. *Science*. **214**, 931–3.
10. Raisman G. 1985. Specialized neuroglial arrangement may explain the capacity of vomeronasal axons to reinnervate central neurons. *Neuroscience*. **14**, 237–54.
11. Tabakow P, Raisman G, Fortuna W, Czyz M, Huber J, Li D, Szewczyk P, Okurowski S, Miedzybrodzki R, Czapiga B, Salomon B, Halon A, Li Y, Lipiec J, Kulczyk A and Jarmundowicz W. 2014. Functional regeneration of supraspinal connections in a patient with transected spinal cord following transplantation of bulbar olfactory ensheathing cells with peripheral nerve bridging. *Cell Transplant*. **23**, 1631–55.
12. Lai C Y, Trewyn B G, Jeftinija D M, Jeftinija K, Xu S, Jeftinija S and Lin V S Y. 2003. A mesoporous silica nanoparticle-based carrier system with chemically removable CdS nanoparticle caps for stimuli-responsive controlled release of neurotransmitters and drug molecules. *J. Am. Chem. Soc.* **125**, 4451–9.
13. Alexander H S. 1962. Biomagnetics—Biological effects of magnetic fields. *Am. J. Med. Electron*. **1**, 181–7.
14. Jackson J D. 1999. *Classical Electrodynamics* (New York: Wiley).
15. Ortega D., in *Magnetic nanoparticles: From fabrication to clinical applications*, edited by N.T.K. Thanh, (CRC Press. Taylor & Francis Group, Boca Raton, FL, 2012). Chapter 1, p. 3. ISBN 9781439869321. 616 Pages.
16. Cullity B D. 1972. *Introduction to Magnetic Materials* (Reading, Mass.: Addison-Wesley Pub. Co.).
17. Seifriz W. 1924. An elastic value of protoplasm, with further observations on the viscosity of protoplasm. *J. Exp. Biol.* **2**, 1–11.
18. Dobson J. 2008. Remote control of cellular behaviour with magnetic nanoparticles. *Nat. Nano* **3**, 139–43.
19. Hallmark B, Darton N J, James T, Agrawal P and Slater N K H. 2010. Magnetic field strength requirements to capture superparamagnetic nanoparticles within capillary flow. *J. Nanopart. Res.* **12**, 2951–65.
20. Frankel R B, Blakemore R P and Wolfe R S. 1979. Magnetite in freshwater magnetotactic bacteria. *Science*. **203**, 1355–6.
21. Buongiorno J. 2005. Convective transport in nanofluids. *J. Heat Transf.* **128**, 240–50.
22. Rogers H B, Anani T, Choi Y S, Beyers R J and David A E. 2015. Exploiting size-dependent drag and magnetic forces for size-specific separation of magnetic nanoparticles. *Int. J. Mol. Sci.* **16**, 20001–19.
23. Kim H K, Hong S H, Hwang S W, Hwang J S, Ahn D, Seong S and Park T H. 2005. Magnetic capture of a single magnetic nanoparticle using nanoelectromagnets. *J. Appl. Phys.* **98**, 104307.
24. Pankhurst Q A, Connolly J, Jones S K and Dobson J. 2003. Applications of magnetic nanoparticles in biomedicine. *J. Phys. D—Appl. Phys.* **36**, R167–R81.
25. Brown W F. 1963 Thermal fluctuations of a single-domain particle. *Phys. Rev.* **130**, 1677–86.
26. Usov N A and Liubimov B Y. 2012. Dynamics of magnetic nanoparticle in a viscous liquid: Application to magnetic nanoparticle hyperthermia. *J. Appl. Phys.* **112**, 11.
27. Lee H, Shin T-H, Cheon J and Weissleder R. 2015. Recent developments in magnetic diagnostic systems. *Chem. Rev.* **115**, 10690–724.
28. Modak N, Datta A and Ganguly R. 2008. Cell separation in a microfluidic channel using magnetic microspheres. *Microfluid. Nanofluid.* **6**, 647.
29. Song H P, Li X G, Sun J S, Xu S M and Han X. 2008. Application of a magnetotactic bacterium, *Stenotrophomonas* sp to the removal of Au(III) from contaminated wastewater with a magnetic separator. *Chemosphere*. **72**, 616–21.
30. Babel S and del Mundo Dacera D. 2006. Heavy metal removal from contaminated sludge for land application: A review. *Waste Manage.* **26**, 988–1004.
31. Gomez-Pastora J, Xue X Z, Karampelas I H, Bringas E, Furlani E P and Ortiz I. 2017. Analysis of separators for magnetic beads recovery: From large systems to multifunctional microdevices. *Sep. Purif. Technol.* **172**, 16–31.
32. Wheeler M A, Smith C J, Ottolini M, Barker B S, Purohit A M, Grippo R M, Gaykema R P, Spano A J, Beenhakker M P, Kucenas S, Patel M K, Deppmann C D and Guler A D. 2016. Genetically targeted magnetic control of the nervous system. *Nat. Neurosci.* **19**, 756.
33. Tenforde T T. 1979. *Magnetic Field Effect on Biological Systems* (USA: Springer).
34. Nakhilni Zn. 1974. Biological effect of constant magnetic fields. *Kosm. Biol. Avia. Med.* **8**, 3–15.
35. Dini L and Abbio L. 2005. Bioeffects of moderate-intensity static magnetic fields on cell cultures. *Micron*. **36**, 195–217.
36. Kirschvink J L, Jones D S and MacFadden B J. 2013. *Magnetite Biomineralization and Magnetoreception in Organisms: A New Biomagnetism*, vol 5 (Berlin, Germany: Springer Science & Business Media).
37. Lerchl A, Nonaka K, Stokkan K-A and Reiter R. 1990. Marked rapid alterations in nocturnal pineal serotonin metabolism in mice and rats exposed to weak intermittent magnetic fields. *Biochem. Biophys. Res. Commun.* **169**, 102–8.
38. Semm P and Demaine C. 1986. Neurophysiological properties of magnetic cells in the pigeon's visual system. *J. Comp. Physiol. A*. **159**, 619–25.
39. Goodman R and Blank M. 1998. Magnetic field stress induces expression of hsp70. *Cell Stress Chaperones*. **3**, 79.
40. Lednev V V. 1991. Possible mechanism for the influence of weak magnetic fields on biological systems. *Bioelectromagnetics*. **12**, 71–5.
41. Miyakoshi J. 2005. Effects of static magnetic fields at the cellular level. *Progr. Biophys. Molec. Biol.* **87**, 213–23.
42. van Deventer E, Simunic D and Repacholi M. 2006. EMF standards for human health. In *Biological and Medical Aspects of Electromagnetic Fields*, BG Frank and S. Barnes, editors. CRC Taylor & Francis Group, Boca Raton, FL. p. 277.
43. Blank M. 1987. Ionic processes at membrane surfaces. In *Mechanistic Approaches to Interactions of Electric and Electromagnetic Fields with Living Systems*, Blank M and Findl E, editors. Springer Science & Business Media, LLC, New York. p. 1.
44. Liboff A R, Smith S D and McLeod B R. 1987. *Mechanistic Approaches to Interactions of Electric and Electromagnetic Fields with Living Systems*, eds M Blank and E Findl (Boston, MA: Springer).
45. Parkinson W C and Sulik G L. 1992. Diatom response to extremely low-frequency magnetic fields. *Radiat. Res.* **130**, 319–30.
46. Sandweiss J. 1990. On the cyclotron resonance model of ion transport. *Bioelectromagnetics*. **11**, 203–5.
47. Dobson J. 2001. Nanoscale biogenic iron oxides and neurodegenerative disease. *FEBS Lett.* **496**, 1–5.
48. Moon W-J, Kim H-J, Roh H G, Choi J W and Han S-H. 2012. Fluid-attenuated inversion recovery hypointensity of the pulvinar nucleus of patients with Alzheimer disease: Its possible association with iron accumulation as evidenced by the T2* map. *Korean J. Radiol.* **13**, 674–83.

49. Maher B A, Ahmed I A, Karloukovski V, MacLaren D A, Foulds P G, Allsop D, Mann D M, Torres-Jardón R and Calderon-Garciduenas L. 2016. Magnetite pollution nanoparticles in the human brain. *Proc. Natl. Acad. Sci.* **113**, 10797–801.
50. Kirschvink J L, Kobayashi-Kirschvink A and Woodford B J. 1992. Magnetite biomineralization in the human brain. *Proc. Natl. Acad. Sci.* **89**, 7683–7.
51. Daley George Q. 2012. The promise and perils of stem cell therapeutics. *Cell Stem Cell.* **10**, 740–9.
52. Li X, Ling W, Khan S, Wang Y P, Pennisi A, Barlogie B, Shaughnessy J and Yaccoby S. 2010. Systemically transplanted human bone marrow mesenchymal stem cells primarily traffic to mesenteric lymph nodes. *Blood.* **116**, 1068.
53. Hohnholt M C, Geppert M and Dringen R. 2011. Treatment with iron oxide nanoparticles induces ferritin synthesis but not oxidative stress in oligodendroglial cells. *Acta Biomater.* **7**, 3946–54.
54. Pinkernelle J, Calatayud P, Goya G F, Fansa H and Keilhoff G. 2012. Magnetic nanoparticles in primary neural cell cultures are mainly taken up by microglia. *BMC Neurosci.* **13**, 32.
55. Tay A, Kunze A, Jun D, Hoek E and Di Carlo D. 2016. The age of cortical neural networks affects their interactions with magnetic nanoparticles. *Small.* **12**, 3559–67.
56. Elder J B, Liu C Y and Apuzzo M L J. 2008. Neurosurgery in the realm of 10(-9), Part 1: Stardust and nanotechnology in neuroscience. *Neurosurgery.* **62**, 1–19.
57. Kumar P, Choonara Y E, Modi G, Naidoo D and Pillay V. 2014. Nanoparticulate strategies for the five R's of traumatic spinal cord injury intervention: Restriction, repair, regeneration, restoration and reorganization. *Nanomedicine.* **9**, 331–48.
58. Goya G F, Marcos-Campos I, Fernandez-Pacheco R, Saez B, Godino J, Asin L, Lambea J, Tabuenca P, Mayordomo J I, Larrad L, Ibarra M R and Tres A. 2008. Dendritic cell uptake of iron-based magnetic nanoparticles. *Cell Biol. Int.* **32**, 1001–5.
59. Kim D H, Rozhkova E A, Ulasov I V, Bader S D, Rajh T, Lesniak M S and Novosad V. 2010. Biofunctionalized magnetic-vortex microdisks for targeted cancer-cell destruction. *Nat. Mater.* **9**, 165–71.
60. Cheng Y, Muroski M E, Petit D, Mansell R, Vemulkar T, Morshed R A, Han Y, Balyasnikova I V, Horbinski C M, Huang X L, Zhang L J, Cowburn R P and Lesniak M S. 2016. Rotating magnetic field induced oscillation of magnetic particles for in vivo mechanical destruction of malignant glioma. *J. Control. Release.* **223**, 75–84.
61. Riggio C, Calatayud M P, Hoskins C, Pinkernelle J, Sanz B, Torres T E, Ibarra M R, Wang L, Keilhoff G, Goya G F, Raffa V and Cuschieri A. 2012. Poly-L-lysine-coated magnetic nanoparticles as intracellular actuators for neural guidance. *Int. J. Nanomed.* **7**, 3155–66.
62. Pickard M R and Chari D M. 2010. Robust uptake of magnetic nanoparticles (MNPs) by central nervous system (CNS) microglia: Implications for particle uptake in mixed neural cell populations. *Int. J. Mol. Sci.* **11**, 967–81.
63. Riggio C, Calatayud M P, Giannaccini M, Sanz B, Torres T E, Fernandez-Pacheco R, Ripoli A, Ibarra M R, Dente L, Cuschieri A, Goya G F and Raffa V. 2014. The orientation of the neuronal growth process can be directed via magnetic nanoparticles under an applied magnetic field. *Nanomed.-Nanotechnol. Biol. Med.* **10**, 1549–58.
64. Dickson B J. 2002. Molecular mechanisms of axon guidance. *Science.* **298**, 1959–64.
65. Daly W, Yao L, Zeugolis D, Windebank A and Pandit A. 2012. A biomaterials approach to peripheral nerve regeneration: Bridging the peripheral nerve gap and enhancing functional recovery. *J. R. Soc. Interface.* **9**, 202–21.
66. Bray D. 1979. Mechanical tension produced by nerve-cells in tissue-culture. *J. Cell Sci.* **37**, 391–410.
67. Pilar Calatayud M, Riggio C, Raffa V, Sanz B, Torres T E, Ricardo Ibarra M, Hoskins C, Cuschieri A, Wang L, Pinkernelle J, Keilhoff G and Goya G F. 2013. Neuronal cells loaded with PEI-coated Fe₃O₄ nanoparticles for magnetically guided nerve regeneration. *J. Mater. Chem. B.* **1**, 3607–16.
68. Pierrat S, Brochard-Wyart F and Nassoy P. 2004. Enforced detachment of red blood cells adhering to surfaces: Statics and dynamics. *Biophys. J.* **87**, 2855–69.
69. Merkel R, Nassoy P, Leung A, Ritchie K and Evans E. 1999. Energy landscapes of receptor-ligand bonds explored with dynamic force spectroscopy. *Nature.* **397**, 50–3.
70. Suter D M and Miller K E. 2011. The emerging role of forces in axonal elongation. *Progr. Neurobiol.* **94**, 91–101.
71. Fass J N and Odde D J. 2003. Tensile force-dependent neurite elicitation via anti-beta1 integrin antibody-coated magnetic beads. *Biophys. J.* **85**, 623–36.
72. Pita-Thomas W, Steketee M B, Moysidis S N, Thakor K, Hampton B and Goldberg J L. 2015. Promoting filopodial elongation in neurons by membrane-bound magnetic nanoparticles. *Nanomedicine.* **11**, 559–67.
73. Steketee M B, Moysidis S N, Jin X L, Weinstein J E, Pita-Thomas W, Raju H B, Iqbal S and Goldberg J L. 2011. Nanoparticle-mediated signaling endosome localization regulates growth cone motility and neurite growth. *Proc. Natl. Acad. Sci. USA.* **108**, 19042–7.
74. Borisova T, Krisanova N, Borsmall u C A, Sivko R, Ostapchenko L, Babic M and Horak D. 2014. Manipulation of isolated brain nerve terminals by an external magnetic field using D-mannose-coated gamma-Fe₂O₃ nano-sized particles and assessment of their effects on glutamate transport. *Beilstein J. Nanotechnol.* **5**, 778–88.
75. Suarato G, Lee S I, Li W, Rao S, Khan T, Meng Y and Shelly M. 2016. Micellar nanocomplexes for biomagnetic delivery of intracellular proteins to dictate axon formation during neuronal development. *Biomaterials.* **112**, 176–91.
76. Roy S, Johnston A H, Newman T A, Glueckert R, Dudas J, Bitsche M, Corbaccella E, Rieger G, Martini A and Schrott-Fischer A. 2010. Cell-specific targeting in the mouse inner ear using nanoparticles conjugated with a neurotrophin-derived peptide ligand: Potential tool for drug delivery. *Int. J. Pharmaceut.* **390**, 214–24.
77. Antman-Passig M and Shefi O. 2016. Remote magnetic orientation of 3D collagen hydrogels for directed neuronal regeneration. *Nano Lett.* **16**, 2567–73.
78. Pinkernelle J, Raffa V, Calatayud M P, Goya G F, Riggio C and Keilhoff G. 2015. Growth factor choice is critical for successful functionalization of nanoparticles. *Front. Neurosci.-Switz.* **9**, 305. doi: 10.3389/fnins.2015.00305
79. Zhang S and Uludag H. 2009. Nanoparticulate systems for growth factor delivery. *Pharmaceut. Res.* **26**, 1561–80.
80. Ziv-Polat O, Shahar A, Levy I, Skaat H, Neuman S, Fregnan F, Geuna S, Grothe C, Haastert-Talini K and Margel S. 2014. The role of neurotrophic factors conjugated to iron oxide nanoparticles in peripheral nerve regeneration: in vitro studies *BioMed Res. Int.* **2014**, 267808.
81. Nadri S, Mahmoudvand H and Eatemadi A. 2016. Magnetic nanogel polymer of bupivacaine for ankle block in rats. *J. Microencapsul.* **33.7**, 656–662.
82. Pilakka-Kanthikeel S, Atluri V S R, Sagar V, Saxena S K and Nair M. 2013. Targeted brain derived neurotropic factors (BDNF) delivery across the blood-brain barrier for neuro-protection using magnetic nano carriers: An in-vitro study. *PLoS One.* **8.4**, e62241.

83. Suri S S, Fenniri H and Singh B. 2007. Nanotechnology-based drug delivery systems. *J. Occup. Med. Toxicol.* **2**, 1.
84. Pardridge W M. 2003. Blood-brain barrier drug targeting: The future of brain drug development. *Molec. Interv.* **3**, 90–105, 51.
85. Sharma H S and Sharma A. 2007. Nanoparticles aggravate heat stress induced cognitive deficits, blood-brain barrier disruption, edema formation and brain pathology. *Progr. Brain Res.* **162**, 245–73.
86. Sun Z, Worden M, Wroczynskyj Y, Yathindranath V, van Lierop J, Hegmann T and Miller D W. 2014. Magnetic field enhanced convective diffusion of iron oxide nanoparticles in an osmotically disrupted cell culture model of the blood-brain barrier. *Int. J. Nanomed.* **9**, 3013–26.
87. Portnoy E, Polyak B, Inbar D, Kenan G, Rai A, Wehrli S L, Roberts T P, Bishara A, Mann A, Shmuel M, Rozovsky K, Itzhak G, Ben-Hur T, Magdassi S, Ekstein D and Eyal S. 2016. Tracking inflammation in the epileptic rat brain by bi-functional fluorescent and magnetic nanoparticles. *Nanomedicine.* **12**, 1335–45.
88. Felgner P L, Gadek T R, Holm M, Roman R, Chan H W, Wenz M, Northrop J P, Ringold G M and Danielsen M. 1987. Lipofection—A Highly Efficient, Lipid-Mediated DNA-Transfection Procedure. *Proc. Natl. Acad. Sci. USA.* **84**, 7413–7.
89. Mah C, Zolotukhin I, Fraites T, Dobson J, Batich C and Byrne B. 2000. Microsphere-mediated delivery of recombinant AAV vectors in vitro and in vivo. *Mol Ther.* **1**, S239.
90. Scherer F, Anton M, Schillinger U, Henkel J, Bergemann C, Kruger A, Gansbacher B and Plank C. 2002. Magnetofection: Enhancing and targeting gene delivery by magnetic force in vitro and in vivo. *Gene Ther.* **9**, 102–9.
91. Furlani E P and Ng K C. 2008. Nanoscale magnetic biotransport with application to magnetofection. *Phys. Rev. E.* **77**, 061914.
92. Adams C F, Pickard M R and Chari D M. 2013. Magnetic nanoparticle mediated transfection of neural stem cell suspension cultures is enhanced by applied oscillating magnetic fields *Nanomed. Nanotechnol. Biol. Med.* **9**, 737–41.
93. Zinder N D and Lederberg J. 1952. Genetic exchange in *Salmonella*. *J. Bacteriol.* **64**, 679–99.
94. Zahid M and Robbins P D. 2012. Protein transduction domains: Applications for molecular medicine. *Curr. Gene Ther.* **12**, 374–80.
95. Campos C, Rocha N B F, Lattari E, Paes F, Nardi A E and Machado S. 2016. Exercise-induced neuroprotective effects on neurodegenerative diseases: the key role of trophic factors. *Exp. Rev. Neurother.* **16**, 723–34.
96. Naldini L, Blomer U, Gally P, Ory D, Mulligan R, Gage F H, Verma I M and Trono D. 1996. In vivo gene delivery and stable transduction of nondividing cells by a lentiviral vector. *Science.* **272**, 263–7.
97. Ellis B L, Hirsch M L, Barker J C, Connelly J P, Steininger R J and Porteus M H. 2013. A survey of ex vivo/in vitro transduction efficiency of mammalian primary cells and cell lines with Nine natural adeno-associated virus (AAV1-9) and one engineered adeno-associated virus serotype. *Virol. J.* **10**, 74.
98. Lim S, Airavaara M and Harvey B K. 2010. Viral vectors for neurotrophic factor delivery: A gene therapy approach for neurodegenerative diseases of the CNS. *Pharmacol. Res.* **61**, 14–26.
99. J I, Goya G F, Pilar Calatayud M, Herenu C B, Reggiani P C and Goya R G. 2012. Magnetic field-assisted gene delivery: Achievements and therapeutic potential. *Curr. Gene Ther.* **12**, 116–26.
100. Hwang J H, Lee S, Kim E, Kim J S, Lee C H, Ahn I S and Jang J H. 2011. Heparin-coated superparamagnetic nanoparticle-mediated adeno-associated virus delivery for enhancing cellular transduction. *Int. J. Pharmaceut.* **421**, 397–404.
101. Pal A, Singh A, Nag T C, Chattopadhyay P, Mathur R and Jain S. 2013. Iron oxide nanoparticles and magnetic field exposure promote functional recovery by attenuating free radical-induced damage in rats with spinal cord transection. *Int. J. Nanomed.* **8**, 2259–72.
102. Stoll G and Bendszus M. 2009. Imaging of inflammation in the peripheral and central nervous system by magnetic resonance imaging. *Neuroscience.* **158**, 1151–60.
103. Horak D, Benes M, Prochazkova Z, Trchova M, Borysov A, Pastukhov A, Paliienko K and Borisova T. 2016. Effect of O-methyl-beta-cyclodextrin-modified magnetic nanoparticles on the uptake and extracellular level of l-glutamate in brain nerve terminals. *Colloids Surf. B Biointerf.* **149**, 64–71.
104. Khuong H T and Midha R. 2013. Advances in nerve repair. *Curr. Neurol. Neurosci. Rep.* **13**, 322.
105. Bunge M B. 2002. Bridging the transected or contused adult rat spinal cord with Schwann cell and olfactory ensheathing glia transplants. *Progr. Brain Res.* **137**, 275–82.
106. Wakao S, Hayashi T, Kitada M, Kohama M, Matsue D, Teramoto N, Ose T, Itokazu Y, Koshino K, Watabe H, Iida H, Takamoto T, Tabata Y and Dezawa M. 2010. Long-term observation of auto-cell transplantation in non-human primate reveals safety and efficiency of bone marrow stromal cell-derived Schwann cells in peripheral nerve regeneration. *Exp. Neurol.* **223**, 537–47.
107. Jenkins S I, Yiu H H, Rosseinsky M J and Chari D M. 2014. Magnetic nanoparticles for oligodendrocyte precursor cell transplantation therapies: Progress and challenges. *Molec. Cell. Ther.* **2**, 23.
108. Bulte J W, Zhang S, van Gelderen P, Herynek V, Jordan E K, Duncan I D and Frank J A. 1999. Neurotransplantation of magnetically labeled oligodendrocyte progenitors: Magnetic resonance tracking of cell migration and myelination. *Proc. Natl. Acad. Sci. USA.* **96**, 15256–61.
109. Franklin R J, Blaschuk K L, Bearchell M C, Prestoz L L, Setzu A, Brindle K M and ffrench-Constant C. 1999. Magnetic resonance imaging of transplanted oligodendrocyte precursors in the rat brain. *Neuroreport.* **10**, 3961–5.
110. Hamasaki T, Tanaka N, Kamei N, Ishida O, Yanada S, Nakanishi K, Nishida K, Oishi Y, Kawamata S, Sakai N and Ochi M. 2007. Magnetically labeled neural progenitor cells, which are localized by magnetic force, promote axon growth in organotypic cocultures. *Spine.* **32**, 2300–9.
111. Riggio C, Nocentini S, Catalayud M P, Goya G F, Cuschieri A, Raffa V and del Rio J A. 2013. Generation of magnetized olfactory ensheathing cells for regenerative studies in the central and peripheral nervous tissue. *Int. J. Molec. Sci.* **14**, 10852–68.
112. Sagar V, Atluri V S R, Pilakka-Kanthikeel S and Nair M. 2016. Magnetic nanotherapeutics for dysregulated synaptic plasticity during neuroAIDS and drug abuse. *Molec. Brain.* **9**, 1, 57.
113. Wu Y-W, Goubran H, Seghatchian J and Burnouf T. 2016. Smart blood cell and microvesicle-based Trojan horse drug delivery: Merging expertise in blood transfusion and biomedical engineering in the field of nanomedicine. *Transf. Apheresis Sci.* **54**, 309–18.
114. Zhang R P, Wang L J, He S, Xie J and Li J D. 2016. Effects of magnetically guided, SPIO-labeled, and neurotrophin-3 gene-modified bone mesenchymal stem cells in a rat model of spinal cord injury. *Stem Cells Int.* **2016**, 2018474.



Dr Gerardo F. Goya (E-mail: goya@unizar.es) is associate professor at the University of Zaragoza, Spain. He has been associate professor at the University of Sao Paulo (Brazil) and he is currently researcher at the Institute of Nanoscience of Aragón (INA), University of Zaragoza. Prof. Goya's pioneering team (<http://www.unizar.es/gfgoya>) on magnetic hyperthermia in Spain established that induced cell death with magnetic hyperthermia without temperature rise is possible. His team has developed engineered MNPs for neural guidance under externally applied magnetic fields. He has over 130 publications on nanomagnetism and bioapplications and holds two patents. Prof. Goya has led the design, development and building of devices for measuring power absorption for magnetic hyperthermia, which established the basis for a spin-off company, nB Nanoscale Biomagnetics, of which he is cofounder and scientific advisor.



Vittoria Raffa holds an MSc in Chemical Engineering, PhD in nanotechnology and is associate professor in molecular biology at the University of Pisa. She is the team leader of the Nanomedicine Lab at the University of Pisa (Department of Biology). Prof. Raffa's research interests include nanomedicine and its applications to molecular biology and neuroscience. She was author in the last 10 years of 60 publications in ISI journals and 5 patents on technologies related to nanomedicine.



Taylor & Francis

Taylor & Francis Group

<http://taylorandfrancis.com>



Taylor & Francis

Taylor & Francis Group

<http://taylorandfrancis.com>

Index

A

Accelerated blood clearance (ABC)
phenomenon, 84

Active pharmaceutical ingredient (API)
manufacturing, 475

AD, *see* Alzheimer's disease (AD), noninvasive guidance scheme of magnetic nanoparticles for drug delivery in

AFM, *see* Atomic force microscopy (AFM)

ALD, *see* Atomic layer deposition (ALD)

Alternating current (AC)
magnetic field, 306
susceptibility, 59

Alternating magnetic fields (AMFs), 161, 462

Alzheimer's disease (AD), noninvasive guidance scheme of magnetic nanoparticles for drug delivery in, 343–363

AD magnetic drug targeting, 357–359

AD and its treatment, 344–347

BBB crossing with magnetic force, 347

best conditions for crossing the BBB, 358–359

electromagnetic actuator for guidance of NPs, 347–350

functionalized magnetic field for sticking prevention and efficient guidance, 351–353

future outlook, 359–360

integration of MPI and magnetic actuation system, 356

magnetic drug delivery to the brain, 347–354

MPI-based real time navigation system, 356–357

Newtonian dynamic model, 353

proposed drug delivery scheme, 347

real-time navigation of MNPs with MPI, 354–357

schematic of MPI-based monitoring, 355–356

simulations of aggregated MNP steering in blood vessels, 353–354

AMFs, *see* Alternating magnetic fields (AMFs)

Ampère's law, 204

Analytical ultracentrifugation (AUC), 109

Antibodies (Abs), 77

API manufacturing, *see* Active pharmaceutical ingredient (API) manufacturing

Apo ferritin, 58

Apoptosis, 455

Arrhenius law, 145

Atomic force microscopy (AFM), 214

Atomic layer deposition (ALD), 259

AUC, *see* Analytical ultracentrifugation (AUC)

B

Bacillus Calmette-Guérin (BCG), 190

Bacteria, magnetotactic, 29, 59, 326–327

BBB, *see* Blood–brain barrier (BBB)

Bioinspired magnetic nanoparticles (MNPs) for biomedical applications, 53–73

animal, MNPs in, 55–56

apoferritin, 58

bioinspired synthesis of MNPs, 58–63

biomineralization of ferritin, synthesis of MNPs inspired by, 58–59

cancer diagnosis and therapy, 63–67

exploring biomineralization for synthesis of high-quality MNPs, 67–68

ferritins, 56–58

future directions, 67–68

genetic engineering for functionalization of bioinspired MNPs for targeted diagnosis and therapy, 68

H-chain ferritin, 53

hyperthermia, 67

in vivo targeting and imaging of microscopic tumours, 64–67

living organisms, MNPs in, 53–58

magnetotactic bacteria, MNPs in, 54–55

magnetotactic bacteria, synthesis of MNPs inspired by, 59–63

peroxidase activity of M-HFn for *in vitro* staining of tumour cells, 63–64

superparamagnetic iron oxide nanoparticles, 53

Biomedical applications, *see* Bioinspired magnetic nanoparticles (MNPs) for biomedical applications; Iron oxide MNPs, controlling the size and shape of (for biomedical applications)

Biomedical diagnosis technology, current progress in magnetic separation (MS)-aided, 175–199

application of HGMS and LGMS in biomedical diagnosis, 181–183

colloidal stability, 188–189

commercialized magnetic particles for magnetic cells separation, 194–196

considerations in design and implementation, 188–194

control parameters, 183–188

high-gradient magnetic concentrator, 181

high-gradient MS, 177–178

hook effect, 188

hydrodynamic effect, 191–192

low-gradient MS, 178–181

magnetic deposition microscopy, 181

neodymium ferrum boron magnet, 177

particle concentration, 185–188

particle shape, 189–190

particle size, 183–185

prozone effect, 188

reversible aggregation, 180

spatial arrangement of magnetic sources, 192–194

specificity, 190–191

working principles of MS, 177–181

Biomedical fields, common magnetic separation in, 229–231

Biosensing, 247–269

atomic layer deposition, 259

background, 248–253

chemical vapour deposition, 259

competition-based magnetic bioassays, 263–264

discrete-time Fourier transform, 257

dual-frequency search coil, 248

Faraday's law of induction, 251

GMR biosensors, 258–265

immunoassays, 261–262

magnetic field sensors for biosensing, 252–253

mercury ions, magnetic detection of, 263

mono-frequency search coil, 248

Néel and Brownian relaxation mechanisms, 249–250

nonlinear magnetic response, 250–252

photolithography, 258

quasi-3D immunoassays, 255–256

search coil biosensors, 248–252, 253–258

superparamagnetism, 248–249

surface biofunctionalization, 259–260

3D immunoassays, 253–255

virus, magnetic detection of, 262–263

viscosity measurements, 256–258

wash-free magnetic bioassay, 264–265

Blood–brain barrier (BBB), 343

Bovine serum albumin (BSA), 187, 382

Brownian forcing, 306

Brownian relaxation time, 147

C

Cancer cells, magnetic separation of exosomes derived from, 236–237

Cancer diagnosis and therapy, bioinspired MNPs for, 63–67

hyperthermia, 67

in vivo targeting and imaging of microscopic tumours, 64–67

peroxidase activity of M-HFn for *in vitro* staining of tumour cells, 63–64

Cancer theranostics based on magnetic nanoparticles, stimuli-regulated, 451–471

alternating magnetic field, 452

apoptosis, 455

external stimuli-triggered theranostics, 452–460

internal stimuli-triggered theranostics, 460–464

light-active theranostics, 459–460

magnetic field-responsive theranostics, 452–459

motional averaging regime, 458

multimodality theranostics, 464

pH-responsive theranostics, 460–463

reactive oxygen species, 455

reduction-responsive theranostics, 463–464

RNA interference, 454

static dephasing regime, 458

thermoablation, 454

Cancer therapy, nanoparticles for nanorobotic agents dedicated to, 319–327

aggregation of nanorobotic agents, 320–321

computerized tomography, 326

Coulomb interaction, 325

diagnostics, 326

- direct drug targeting, 319
 - electromagnetic actuation systems, 321
 - hyperthermia produced by MNPs in nanorobotic agents, 323–324
 - Lenz law, 324
 - localization of MNPs, 322
 - magnetic NPs used by nanorobotic agents, 320
 - magnetic particle imaging, 323
 - magnetic resonance imaging, 322–323
 - magnetic resonance navigation, 321
 - magnetosome island, 327
 - magnetotactic bacteria, 326–327
 - microencapsulation, 325
 - navigation and targeting methods for MNPs, 321–322
 - oil in water emulsion, 325
 - photo-acoustic imaging, 326
 - positron emission tomography, 326
 - radio frequency oscillating magnetic field, 322
 - shear-focusing methods, 325
 - therapeutic index, 319
 - ultrasound, 326
 - water in oil emulsion, 325
 - Cancer treatment using magnetic hyperthermia (MHT), 305–316
 - assessment of heating efficiency of magnetic nanoparticles *in vitro*, 308–310
 - Brownian forcing, 306
 - chemotherapy, MHT and, 312–313
 - dynamic magnetic susceptibility, 307
 - future perspectives, 313
 - heating efficiency of MNPs immobilized in tumours, 310
 - immunomodulation, MHT and, 313
 - interactions between magnetic nanoparticles and alternating magnetic fields, 305–307
 - MHT used in combination with other approaches for cancer treatment, 310–313
 - Néel forcing, 306
 - radiotherapy, MHT alone and in combination with, 312
 - requisites for efficient magnetic hyperthermia in biological contexts, 307–310
 - zero-field Brownian relaxation, 306
 - zero-field Néel relaxation, 306
 - Carbon-coated magnetic metal nanoparticles for clinical applications, 43–51
 - application of specific surface functionalizations, 45–46
 - blood purification, future of carbon-coated metal nanomagnets in, 47–49
 - carbon nanotubes, 43
 - diagnostics, carbon-coated metal nanomagnets for, 46–47
 - future outlook, 49
 - initial chemical derivatization of the carbon surface, 45
 - physical properties, 43–45
 - surface initiated atom transfer radical polymerization, 46
 - synthesis of carbon-coated nanomagnets, 43
 - Carbon nanotubes (CNTs), 43
 - Catecholamines, 153
 - Cellular organelles, 231
 - Central nervous system (CNS), 396
 - Chemical vapour deposition (CVD), 259
 - Chemotherapy, hyperthermia and, 312, 336
 - Chitosan, 15
 - Circulating tumour cells (CTCs), 202, 221–222
 - Clinical applications, *see* Carbon-coated magnetic metal nanoparticles for clinical applications; Scalable magnetic nanoparticle synthesis and surface functionalization for clinical applications (experimental considerations for)
 - CNS, *see* Central nervous system (CNS)
 - CNTs, *see* Carbon nanotubes (CNTs)
 - Coarse-grain (CG) model, 179
 - Colloidal nanoclusters (CNC), 29
 - Complex media, magnetic particle transport in, 381–392
 - combined fields to enhance transport, 385–386
 - engineering the interface, 381–382
 - future directions, 389
 - helices, 387–389
 - nonspherical particles in viscoelastic biomaterials, 386–389
 - particle motion in three model biological polymers, 382–385
 - rods, 386–387
 - rolled up sheets for drilling, 389
 - salient features of viscoelastic environments, 383
 - step-out frequency, 388
 - transport through the extracellular matrix, 383–384
 - transport through mucus, 384
 - transport through the skin, 384–385
 - Computed tomography (CT), 326, 458
 - Coulomb interaction, 325
 - Critical quality attributes (CQA), 476
 - CSNPs, *see* Silica-coated iron oxide nanoparticles (CSNPs)
 - CTCs, *see* Circulating tumour cells (CTCs)
 - Curie's law, 144
 - Current GMP (cGMP), 475
 - CVD, *see* Chemical vapour deposition (CVD)
 - Cyclic RGD (Arg-Gly-Asp) peptide (cRGD), 37
- D**
- DDT, *see* Direct drug targeting (DDT)
 - Degrees of freedom (DOF), 321
 - DFT, *see* Discrete-time Fourier transform (DFT)
 - Differential centrifugal sedimentation (DCS), 109
 - Dipolar-hard-sphere model (DHS), 26
 - Dipole–dipole interactions, 25, 27, 147
 - Direct drug targeting (DDT), 319
 - Discrete-time Fourier transform (DFT), 257
 - DLE, *see* Drug loading efficiency (DLE)
 - DMS, *see* Dynamic magnetic susceptibility (DMS)
 - DOF, *see* Degrees of freedom (DOF)
 - Drug delivery, *see* Alzheimer's disease (AD), noninvasive guidance scheme of magnetic nanoparticles for drug delivery in; On-demand drug delivery device, magnetic porous PDMS as
 - Drug delivery systems (DDS), 412
 - Drug loading efficiency (DLE), 161–162
 - Drugs, encapsulation and release of drugs (from magnetic silica nanocomposites), 161–172
 - design of magnetic core MS shell nanoparticles, 163–165
 - drug loading in bare MS shell (colloidal stability), 165
 - drug loading in magnetic core–mesoporous silica shell nanoparticles, 163–166
 - drug sequestration/coupling, 162
 - encapsulation by in situ sol–gel process, 162–163
 - gatekeeping strategies for stimuli responsive drug release, 167–169
 - influence of chemical surface modification on drug loading and release, 166–167
 - light-responsive release from drug-loaded magnetic silica, 169
 - lower critical solution temperature, 168
 - magnetothermal responsive drug release via thermoresponsive gatekeepers, 168
 - nonporous magnetic silica composites with drug release actuated by magnetothermal effects, 162–163
 - pH-responsive release from drug-loaded magnetic silica, 169
 - polymer grafting, improving colloidal stability by, 165–166
 - tailoring drug loading/release by electrostatic attractions, 166
 - tailoring drug loading/release by π – π stacking interactions, 166–167
 - tailoring drug loading/release by tuning H-bond interactions, 167
 - thermodegradable bond, 168
 - Dulbecco's modified Eagle medium (DMEM), 46
 - Dynamic light scattering (DLS), 109
 - Dynamic magnetic susceptibility (DMS), 307
- E**
- ECM, *see* Extracellular matrix (ECM)
 - Effective-one-spin (EOS) models, 26
 - Electromagnetic actuation (EMA) systems, 321
 - Electromagnets, 202
 - Electron energy loss spectroscopy (EELS), 109
 - Emulsion–solvent–evaporation process (ESE), 15
 - Endosomes, magnetic separation of, 233–235
 - Energy dispersive X-ray spectroscopy (EDX), 109
 - Enhanced permeability and retention (EPR) effect, 83, 412
 - Enzyme-linked immunosorbent assays (ELISAs), 347
 - EOS models, *see* Effective-one-spin (EOS) models
 - ETH start-up Hemotune, 49
 - Exosomes, magnetic separation of, 236–239
 - Extended Derjaguin–Landau–Verwey–Overbeek (XDLVO) analysis, 179
 - Extracellular matrix (ECM), 103, 383–384
- F**
- FACS, *see* Fluorescence-activated cell sorting (FACS)
 - Faraday's law, 251, 322
 - FBS, *see* Foetal bovine serum (FBS)
 - Ferrimagnetism, 397
 - Ferritins, 56–58
 - Ferrofluids, 436
 - Fibroblast activation protein- α (FAP- α), 65
 - Field function (FF), 344
 - Fluorescence-activated cell sorting (FACS), 219

Fluorescence resonance energy transfer (FRET), 281
 Foetal bovine serum (FBS), 276
 Food and Drug Administration (FDA), 325, 475
 Fourier transform IR spectroscopy (FTIR), 110

G

Giant magnetoresistor (GMR), 247
 GMR biosensors, 258–265
 atomic layer deposition, 259
 chemical vapour deposition, 259
 competition-based magnetic bioassays, 263–264
 detection principle, 260–261
 fabrication, 258–259
 immunoassays, 261–262
 mercury ions, magnetic detection of, 263
 photolithography, 258
 surface biofunctionalization, 259–260
 virus, magnetic detection of, 262–263
 wash-free magnetic bioassay, 264–265
 Gold nanoparticles, 104, 305
 Good manufacturing practices (GMP), 475–482
 active pharmaceutical ingredient manufacturing, 475
 background and driving forces, 475–476
 critical quality attributes, 476
 from research and development to GMP environment, 476–479
 prerequisites of GMP conformed manufacturing, 479–482
 quality, 475
 quality control analytics, 480–482
 quality by design, 478–479
 requirements, 476
 scale-up, 478
 site master file, 476

H

Hard magnetic materials, 202
 H-chain ferritin (HFn), 53
 High-angle annular dark field (HAADF), 57
 High-gradient magnetic concentrator (HGMC), 181
 High-gradient MS (HGMS), 177–178
 High-resolution transmission electron microscopy (HRTEM), 57
 HLB, *see* Hydrophilic–lipophilic balance (HLB)
 Hook effect, 188
 Horseradish peroxidase (HRP), 63
 Human health, impact of core and functionalized magnetic nanoparticles on, 289–303
 degradation of IONPs, 290
 exposure conditions used, influence of, 297–298
 future outlook, 299
 influence of the size and shape of IONPs, 297
 intracellular IONP levels and cellular responses, 290–293
 IONP toxicity overview, 289–293
 magnetic core, influence of, 293
 reactive oxygen species, induction of, 290
 surface coatings, influence of, 293–297
 Hydrodynamic focusing, 219
 Hydrophilic–lipophilic balance (HLB), 86
 Hyperthermia, *see* Magnetic hyperthermia, smart nanoparticles and the effects in (*in vivo*)

I

IAVs, *see* Influenza A viruses (IAVs)
 ICAM-1, *see* Intercellular adhesion molecule 1 (ICAM-1)
 IGF-I, *see* Insulin-like growth factor I (IGF-I)
 Immune cells, magnetic separation of exosomes derived from, 237–238
 Immunoglobulin G (IgG), 81
 Immunomodulation, MHT and, 313
 Influenza A viruses (IAVs), 262
 Insulin-like growth factor I (IGF-I), 404
 Integrated micro-analytical systems, magnetic separation in, 201–227
 actively controlled magnets, 203–204
 actively controlled magnets used in separation systems, 210–217
 applications, 217–224
 bacteria and viruses, 218
 blood cells, 221
 capture rate, 221
 cell separation (alternative methods), 218–219
 cell separation (analysis beyond magnetic separation), 222–224
 cell separation (cells sorted in immunomagnetic separation), 221–222
 cell separation (methods of magnetic labelling), 219–221
 circulating tumour cells, 202, 221–222
 DNA/RNA, 217–218
 electromagnets, 202
 fluorescence-activated cell sorting, 219
 future perspectives, 224
 hard magnetic materials, 202
 hydrodynamic focusing, 219
 magnetic carriers, 202–203
 magnetic carriers used in magnetic separation systems, 205–208
 magnetic field intensity, 204
 magnetic force, 204
 magnetic labelling, 204
 magnetic separation, 204–205
 magnetic separation, applications of, 217–218
 magnetization, 202–204
 materials, 205–217
 microfluidic separation, 219
 permanent magnets, 203
 permanent magnets used in separation systems, 208–210
 principles, 202–205
 proteins, 217
 size of magnetic carriers, 204–205
 soft lithography technique, 211
 soft magnetic materials, 202
 stem cells, 221
 superparamagnetism, 202
 Intercellular adhesion molecule 1 (ICAM-1), 87
 Internal stimuli-triggered theranostics, 460–464
 pH-responsive theranostics, 460–463
 reduction-responsive theranostics, 463–464
 Iron oxide MNPs, controlling the size and shape of (for biomedical applications), 3–22
 aqueous synthesis, 4–8
 biomineralization, 7–8
 chitosan, 15
 co-precipitation of iron (II) and (III) salts, 5–6
 electrochemical synthesis, 13–14
 emulsion–solvent–evaporation process, 15
 microwave-assisted synthesis, 11–13

miscellaneous synthetic routes, 14
 organic synthesis by thermal decomposition of organic precursor, 8–10
 partial oxidation of iron (II) salts, 6
 partial reduction of iron (III) salts, 6
 particles' coating and polymer encapsulation, 14–15
 polyol synthesis, 10–11
 reduction of antiferromagnetic precursor, 6–7
 specific microwave effects, 13
 state of the art, 3–4
 synthesis routes, progress on, 4–14
 Iron oxide nanoparticles (IONPs), 97, 139, 161, 289
 Iron oxide nanoparticles (IONPs), immunotoxicity and safety considerations for, 273–286
 blood compatibility, 281–282
 clinical application, 273–274
 coagulation system, 274–275
 efficient design of IO formulations, 282–283
 endotoxin contamination and sterility, 278
 future perspectives, 283
 haemolysis, 275
 immune system, 277–278
 immunotoxicity and safety issues associated with IONP, 274–278
 improving early design, assessment and safety considerations, 282–283
 main elements of immunotoxicity assessment, 278–282
 opsonization and monocyte–phagocytic system, 275–276
 protein corona, 276–277

L

LAL assay, *see* Limulus amoebocyte lysate (LAL) assay
 LCST, *see* Lower critical solution temperature (LCST)
 LDL, *see* Low-density lipoprotein (LDL)
 Lenz law, 324
 LGMS, *see* Low-gradient MS (LGMS)
 Light-active theranostics, 459–460
 image-guided therapy, 460
 light-triggered delivery, 460
 photodynamic therapy, 459–460
 photothermal therapy, 459
 Limits of detections (LODs), 255, 262
 Limulus amoebocyte lysate (LAL) assay, 279
 Lipopolysaccharides (LPS), 49
 Living organisms, MNPs in, 53–58
 animal, MNPs in, 55–56
 ferritins, 56–58
 magnetotactic bacteria, MNPs in, 54–55
 Localized surface plasmon resonance (LSPR) biosensing, 231
 LODs, *see* Limits of detections (LODs)
 Low-density lipoprotein (LDL), 233
 Lower critical solution temperature (LCST), 168
 Low-gradient MS (LGMS), 178–181
 LPS, *see* Lipopolysaccharides (LPS)
 LSPR biosensing, *see* Localized surface plasmon resonance (LSPR) biosensing

M

MAbs, *see* Monoclonal Abs (MAbs)
 Magnetic deposition microscopy (MDM), 181

- Magnetic hyperthermia, smart nanoparticles and the effects in (*in vivo*), 331–340; *see also* Cancer treatment using magnetic hyperthermia (MHT)
- actively targeted NPs in the tumour site for magnetic hyperthermia, 335–336
 - combination of hyperthermia with chemotherapy and radiotherapy, 336–337
 - combining magnetic hyperthermia with MRI, 336
 - future outlook, 338
 - impact of heating on target tumour cells, 333
 - magnetic field applicators for magnetic hyperthermia, 332
 - NP specifications for magnetic hyperthermia, 331–332
 - passive targeting of NPs for magnetic hyperthermia, 335
 - temperature distribution in the tumour region, 333–334
 - therapeutic strategies of hyperthermia *in vivo*, 334–336
- Magnetic nanochains, *see* Nanochains (NCs)
- Magnetic nanoparticles (NPs), properties and interactions of, 26–29
- colloidal nanoclusters, 29
 - dipolar-hard-sphere model, 26
 - dipolar interactions, 27–28
 - effective-one-spin models, 26
 - experimental evidence of dipolar behavior, 28–29
 - interactions between particles, 27
 - isolated magnetic NPs, 26–27
 - magnetic properties at the nanometric scale, 26
- Magnetic particle imaging (MPI), 344
- Magnetic resonance imaging (MRI)
- carbon-coated metallic nanoparticles and, 47
 - combining magnetic hyperthermia with, 336
 - contrast agents, 37, 77, 129
 - principles of, 141–143
- Magnetic resonance navigation (MRN), 321
- Magnetic separation (MS), 175
- Magnetoferritin (M-HFn) nanoparticles, 53
- Magnetopolymerosomes, 124–133
- approaches to encapsulate iron oxide nanoparticles in polymerosomes, 124–127
 - characterization, 128–129
 - microscopy techniques, 128–129
 - as MRI contrast agents, 129–131
 - as nanotheranostic systems, 132–133
 - scattering methods, 128
 - small particles of iron oxide, 124
 - ultrasmall superparamagnetic iron oxide nanoparticles, 124
- Magnetosome island (MAI), 327
- Magnetotactic bacteria, 29, 59, 326–327
- Magnetotransduction, 404
- MAR, *see* Motional averaging regime (MAR)
- Maximum safe concentration (MSC), 366
- MDDCs, *see* Monocyte-derived dendritic cells (MDDCs)
- MDM, *see* Magnetic deposition microscopy (MDM)
- MEC, *see* Minimum effective concentration (MEC)
- Mercury ions, magnetic detection of, 263
- Mesoporous silica (MS), 163
- M-HFn nanoparticles, *see* Magnetoferritin (M-HFn) nanoparticles
- Micro-analytical systems, *see* Integrated micro-analytical systems, magnetic separation in
- Minimum effective concentration (MEC), 366
- Mitochondria, magnetic separation of, 239–240
- Mitomycin-C (MMC), 310
- Monoclonal Abs (MAbs), 84
- Monocyte-derived dendritic cells (MDDCs), 185
- Mononuclear phagocyte system (MPS), 83
- Monte Carlo (MC) simulations, 27
- Motional averaging regime (MAR), 458
- MPI, *see* Magnetic particle imaging (MPI)
- MRI, *see* Magnetic resonance imaging (MRI)
- MRI applications, *see* Polymerosomes for MRI and theranostic applications; Ultrasmall iron oxide nanoparticles (IONPs) stabilized with multidentate polymers for applications in MRI
- MRN, *see* Magnetic resonance navigation (MRN)
- Multidentate block copolymer (MDBC), 140
- Multidentate polymers, *see* Ultrasmall iron oxide nanoparticles (IONPs) stabilized with multidentate polymers for applications in MRI
- ## N
- Nanochains (NCs), 25–41
- antibacterial properties, 38
 - applications, 37–38
 - biomarkers and MRI contrast agents, 37
 - chemical synthesis, 34–36
 - colloidal nanoclusters, 29
 - dipolar behavior, experimental evidence of, 28–29
 - dipolar-hard-sphere model, 26
 - dipolar interactions, 27–28
 - dipole–dipole interactions, 25, 27
 - effective-one-spin models, 26
 - external magnetic field, application of 30–34
 - future directions, 38–39
 - individual magnetic NPs, 37
 - interactions between particles, 27
 - isolated magnetic NPs, 26–27
 - magnetic electrospeaking, 36–37
 - magnetic nanoparticles (NPs), properties and interactions of, 26–29
 - magnetic properties at the nanometric scale, 26
 - magnetotactic bacteria, 29
 - microfluidics, 37
 - nanomedicine, 37
 - nanopeapod, 36
 - nanoworms, 34
 - 1-D assemblies (life sciences), 37
 - regenerative medicine, 38
 - self-assembly, 29–30
 - self-assembly induced by external forces or constraints, 30–37
 - synthetic strategies, 29–37
 - therapy (delivery of medicines and hyperthermia), 37–38
 - X-ray diffraction pattern, 35
- Nanomedicine, 37
- Nanopeapod, 36
- Nanorobotic agents, *see* Cancer therapy, nanoparticles for nanorobotic agents dedicated to
- Nanowire (NW) formation, 33
- Nanoworms, 34
- Near-infrared (NIR) emitting probes, 412
- Near-infrared fluorescence (NIRF), 65, 418
- Néel–Arrhenius law, 249
- Néel forcing, 306
- Néel relaxation time, 145
- Neodymium ferrum boron (NdFeB) magnet, 177
- Nerve guidance conduits (NGCs), 395
- Neural engineering, 395–408
- cell therapies, 405
 - effects of DC magnetic fields on neural cells, 399–400
 - electromagnetic theory, 399
 - ferrimagnetism, 397
 - historical summary and state of the art, 395–396
 - instrumentation, 398–399
 - magnetic actuation on neural cells, 399–401
 - magnetic field–magnetic nanoparticle interactions, 397
 - magnetic forces can actuate on cells, 400–401
 - magnetic guidance, 401–402
 - magnetism of single-domain nanoparticles, 396–399
 - magnetofection, 402–404
 - magnetoreception, 399
 - magnetotransduction, 404
 - nerve repair, 401–405
 - neuroprotection, 402
 - outlook for the future, 405
 - physical features of magnetic nanoparticles, 397–398
 - scavenging strategies, 404–405
 - superparamagnetism, 397
- NGCs, *see* Nerve guidance conduits (NGCs)
- NIR emitting probes, *see* Near-infrared (NIR) emitting probes
- NIRF, *see* Near-infrared fluorescence (NIRF)
- Nonmuscle-invasive bladder cancer (NMIBC), 310
- Nuclear magnetic relaxation dispersion (NMRD) profiling, 149
- Nuclear magnetic relaxation (NMR) observables, 148
- Nuclear magnetic resonance (NMR) spectroscopy, 110
- ## O
- Oil in water (O/W) emulsion, 325
- Oleic acid (OA), 31, 144
- Olfactory ensheathing cells (OECs), 396
- On-demand drug delivery device, magnetic porous PDMS as, 365–379
- active controlled delivery of drugs, 367–368
 - characterization of magnetic porous PDMS, 370–371
 - controlled docetaxel release, 375–377
 - controlled drug release system, 366
 - current challenges, 369
 - device characterization, 374
 - docetaxel release, 374
 - drug delivery device fabrication, 371–374
 - electrical stimuli, 367
 - localized drug delivery, 366
 - magnetic porous PDMS, 369–370
 - magnetic sponge as on-demand drug delivery device, 369
 - magnetic stimuli, 367–368
 - materials and methods, 369–374
 - methylene blue release, 374–375
 - osmosis-based methods, 367

- passive controlled delivery of drugs, 366–367
 polymeric drug delivery, 366–367
 porous PDMS, 369
 reservoir-based drug delivery devices, 367
 results and discussions, 374–377
- Opsonins, 83
- Organelle separation, 229–245
 biomedical fields, common magnetic separation in, 229–231
 cancer cells, magnetic separation of
 exosomes derived from, 236–237
 cells and bacteria, magnetic separation of, 229–230
 different states of endosomes, magnetic separation of, 234–235
 endosomes, magnetic separation of, 233–235
 exosomes, magnetic separation of, 236–239
 future outlook, 242
 immune cells, magnetic separation of
 exosomes derived from, 237–238
 importance of magnetic separation of
 cellular organelles, 231–232
 localized surface plasmon resonance biosensing, 231
 magnetic–plasmonic hybrid nanoparticles, 241–242
 magnetic separation and simultaneous
 detection of exosomes, 239
 mitochondria, magnetic separation of, 239–240
 mouse tissues, magnetic separation of
 mitochondria derived from, 239–240
 multifunctional nanoparticles for versatile
 isolation of cellular organelles, 240–242
 proteins, magnetic separation of, 230–231
 receptor-mediated endosomes, magnetic separation of, 235
 requirements for magnetic probes for
 versatile isolation of cellular organelles, 240–241
 sedimentation equilibrium, 232
 velocity sedimentation, 232
- P**
- PAA polymer, *see* Polyacrylic acid (PAA) polymer
 PAI, *see* Photo-acoustic imaging (PAI)
 PA nanofibers, *see* Peptide-amphiphile (PA) nanofibers
 PC, *see* Protein corona (PC)
 PDI, *see* Polydispersity index (PDI)
 PDMS, *see* On-demand drug delivery device, magnetic porous PDMS as
 PEGylation, 83
 Peptide-amphiphile (PA) nanofibers, 32
 Peripheral nervous system (PNS), 395
 PET, *see* Positron emission tomography (PET)
 Phosphate buffered saline (PBS), 46
 Photo-acoustic imaging (PAI), 326
 Photolithography, 258
 pH-responsive theranostics, 460–463
 PNS, *see* Peripheral nervous system (PNS)
 Point-of-care (POC) devices, 248
 Polyacrylic acid (PAA) polymer, 31
 Polydispersity index (PDI), 103
 Polymersomes for MRI and theranostic applications, 121–136
 abbreviations, 133–134
 approaches to encapsulate iron oxide nanoparticles in polymersomes, 124–127
 biomedical applications, polymersomes for, 121–123
 general introduction to polymersomes, 121–122
 magnetopolymersomes, 124–133
 mononuclear phagocytic system, 123
 MRI contrast agents, magnetopolymersomes as 129–131
 nanotheranostic systems, magnetopolymersomes as, 132–133
 outlook, 133
 polymersomes in biomedical research, 123
 polymersomes preparation techniques, 122–123
 polymersomes vs. liposomes, 123
 reticuloendothelial system, 123
 small particles of iron oxide, 124
 ultrasmall superparamagnetic iron oxide nanoparticles, 124
 Positron emission tomography (PET), 326, 412, 458
 Product quality review (PQR), 475
 Protein corona (PC), 276–277, 309
 Prozone effect, 188
- Q**
- Quality assurance (QA), 475
 Quality control (QC), 475
 Quality management (QM), 475
 Quantitative nanostructure–activity relationships (QNAR), 88
- R**
- Rabbit pyrogen test (RPT), 279
 Radio frequency (RF) oscillating magnetic field, 322
 Radiofrequency (RF) wave, 139
 Radionuclide labeling and imaging of magnetic nanoparticles, 411–429
 drug delivery systems, 412
 enhanced permeability and retention effect, 412
 formation of a radiolabeled MNP, 415–420
 future perspective, 423–424
 imaging methods to label NPs and track them *in vivo*, 414–423
 in vivo imaging evaluation studies, 420–422
 multimodal imaging of NPs, 412–413
 near-infrared emitting probes, 412
 new applications, 423
 nuclear imaging in preclinical studies of NPs, 413–414
 role of imaging in development of magnetic nanoparticles for diagnostic and therapeutic applications, 411–414
 translation to human clinical trials, 422–423
 Radiotherapy, hyperthermia and, 312, 336
 Reactive oxygen species (ROS), 290, 455
 Red blood cells (RBCs) constructs to prolong the life span of iron-based MRI/MPI contrast agents *in vivo*, 431–449
 challenges and outlook, 445
 ferrofluids, 436
 in vivo delivery of MNPs by RBCs, 440–442
 loading procedures for SPION encapsulation in RBCs, 436–438
 not all SPION NPs can be encapsulated into RBCs, 438–440
 red blood cells, 431–432
 SPIO-loaded RBCs as tracers, 442–445
 strategies for SPION carriage by RBCs, 435–436
 use of RBCs to deliver SPIO- and USPIO-based NPs, 432–442
 Reduction-responsive theranostics, 463–464
 Relaxivity, theory of, 147
 Reservoir-based drug delivery devices, 367
 Reticuloendothelial system (RES), 83, 104
 Reversible aggregation, 180
 RFLP (restriction fragment length polymorphism), 281
 RNA interference, 454
 ROS, *see* Reactive oxygen species (ROS)
 RPT, *see* Rabbit pyrogen test (RPT)
- S**
- SANS, *see* Small-angle neutron scattering (SANS)
 SAR, *see* Specific absorption rate (SAR)
 SAXS, *see* Small-angle X-ray scattering (SAXS)
 Scalable magnetic nanoparticle synthesis and surface functionalization for clinical applications (experimental considerations for), 97–120
 analytical ultracentrifugation, 109
 batch techniques, 98–99
 biological functionalization, 103–109
 chemical measurements, 110–111
 continuous characterization techniques, 111–112
 continuous techniques, 99–100
 differential centrifugal sedimentation, 109
 dynamic light scattering, 109
 electron energy loss spectroscopy, 109
 energy dispersive X-ray spectroscopy, 109
 extracellular matrix, 103
 impact of functionalization on MNPs and cell–NP interactions, 108–109
 iron oxide nanoparticles, 97
 methods of characterization for particles and surface functionalization, 109–112
 negative staining, 109
 outlook, 112
 particle size and hydrodynamic radius measurements, 109–110
 polydispersity index, 103
 scale up of NP synthesis, 98–100
 small-angle neutron scattering, 109
 small-angle X-ray scattering, 109
 stabilization and functionalization of MNPs, 100–112
 thermogravimetric analysis, 109
 transmission electron microscopy, 109
 Scanning electron microscopy (SEM), 214, 436
 SCI, *see* Spinal cord injury (SCI)
 SDR, *see* Static dephasing regime (SDR)
 SEA, *see* Staphylococcal enterotoxin A (SEA)
 Search coil biosensors, 248–252, 253–258
 discrete-time Fourier transform, 257
 quasi-3D immunoassays, 255–256
 search coil-based immunoassays, 253
 3D immunoassays, 253–255
 viscosity measurements, 256–258
 Sedimentation equilibrium, 232
 Shear-focusing methods, 325
 SI-ATRP, *see* Surface initiated atom transfer radical polymerization (SI-ATRP)
 Silica-coated iron oxide nanoparticles (CSNPs), 185

- Silica nanocomposites, *see* Drugs, encapsulation and release of drugs (from magnetic silica nanocomposites)
- Single-photon emission computed tomography (SPECT), 106, 412
- Site master file (SMF), 476
- Small-angle neutron scattering (SANS), 109
- Small-angle X-ray scattering (SAXS), 109
- Small particles of iron oxide (SPIOs), 124
- SMF, *see* Site master file (SMF)
- Soft lithography technique, 211
- Soft magnetic materials, 202
- Solomon–Bloembergen–Morgan (SBM) theory, 147
- Specific absorption rate (SAR), 67
- SPECT, *see* Single-photon emission computed tomography (SPECT)
- Spinal cord injury (SCI), 396
- Staphylococcal enterotoxin A (SEA), 255
- Static dephasing regime (SDR), 458
- Stem cells, 221
- Stokes law, 177, 204, 397
- Superconducting quantum interference device (SQUID), 111, 247
- Superparamagnetic iron oxide (SPIO) nanoparticles, 53
- Superparamagnetic iron oxide nanoparticles (SPIOs), 452
- Superparamagnetic nanoparticle (SPION), 30, 249
- Superparamagnetism, 202, 248, 397
- Surface biofunctionalization for *in vivo* targeting of magnetic nanoparticles (MNPs), 77–94
- abbreviations, 88–89
 - accelerated blood clearance phenomenon, 84
 - anchoring groups, 80–81
 - basic principles, 78–82
 - current challenges in MNP bioconjugation for *in vivo* targeting, 84–88
 - effect of bioconjugation on physicochemical parameters of NP surface, 86
 - effect of multivalence on affinity/avidity and specificity, 87
 - enhanced permeation and retention effect, 83
 - future outlook, 88
 - hydrophilic–lipophilic balance, 86
 - inorganic coating, 81
 - intercellular adhesion molecule 1, 87
 - ligand orientation, 86–87
 - main critical parameters involved in active targeting approaches, 86–87
 - mononuclear phagocyte system, 83
 - nano–bio interface, 82–84
 - nucleic-acid-based ligands, 84–85
 - opsonins, 83
 - PEGylation, 83
 - peptides, 85
 - polymers, 81
 - preassessment of targeting efficiency, 87–99
 - proteins, 85
 - shielding approaches, 83–84
 - small molecules, 85–86
 - specification analysis for *in vivo* applications of bioconjugated MNPs, 82–83
 - subsequent relevant prefunctionalization steps, 79–81
 - surface types of MNPs as a function of synthetic methods, 78
 - synthetic strategies for bioconjugation, 82
 - targeting-by-design, 88
 - targeting ligands, 84–86
- Surface functionalization, *see* Scalable magnetic nanoparticle synthesis and surface functionalization for clinical applications (experimental considerations for)
- Surface initiated atom transfer radical polymerization (SI-ATRP), 46
- T**
- Targeted drug delivery (TDD), 343
- Targeting-by-design, 88
- TEM, *see* Transmission electron microscopy (TEM)
- Theranostics, *see* Cancer theranostics based on magnetic nanoparticles, stimuli-regulated; Polymersomes for MRI and theranostic applications
- Thermal therapy, *see* Magnetic hyperthermia, smart nanoparticles and the effects in (*in vivo*)
- Thermoablation, 454
- Thermogravimetric analysis (TGA), 109
- Toxic shock syndrome toxin (TSST), 255
- Transferrin receptor 1 (TfR1), 63, 85
- Transmission electron microscopy (TEM), 29, 59, 109, 309
- U**
- Ultrasmall iron oxide nanoparticles (IONPs) stabilized with multidentate polymers for applications in MRI, 139–160
- Arrhenius law, 145
 - Brownian relaxation time, 147
 - catecholamines, 153
 - coordinated water residence time, 149
 - Curie's law, 144
 - dipole–dipole interactions, 147
 - electron relaxation times, 149
 - from spin relaxation to MRI signal, 142–143
 - hydration number, 149
 - main parameters affecting relaxivity of contrast agents, 149
- MDBC stabilization strategy, 150–155
- molecular coatings and ligands developed for individualised USPIOs, 151–152
- MRI, principles of, 141–143
- multidentate polymers for high-stability USPIO coatings, 152–155
- Néel relaxation time, 145
- nuclear magnetic relaxation dispersion profiling, 149
- nuclear magnetic relaxation observables, 148
- oleic acid, 144
- OS relaxation and superparamagnetic nanoparticles, 149
- paramagnetic contribution to relaxivity, 148–149
- relaxometric properties of ultra-small IONPs, 147–150
- rotational correlation time, 149
- structure and magnetic properties of ultrasmall IONPs, 144–147
- superparamagnetic nanoparticles and measurement of relaxivity by NMRD, 149–150
- theory of relaxivity and its practical aspects, 147–148
- T1 and T2 relaxation, 141–142
- ultrasmall ionps for T1-weighted MRI, 150–151
- Ultrasmall superparamagnetic iron oxide nanoparticles (USPIO), 124, 140, 432; *see also* Ultrasmall iron oxide nanoparticles (IONPs) stabilized with multidentate polymers for applications in MRI
- Ultrasound (US), 326
- Ultraviolet (UV) lamp irradiation, 81
- Ultraviolet (UV) spectroscopy, 58
- V**
- van der Waals (VdW) forces, 79
- Velocity sedimentation, 232
- Virus, magnetic detection of, 262–263
- W**
- Water in oil (W/O) emulsion, 325
- X**
- X-ray diffraction (XRD) pattern, 35
- X-ray photo-electron spectroscopy (XPS), 110
- Z**
- Zero-field Brownian relaxation, 306
- Zero-field Néel relaxation, 306