Therapeutic Applications of Cell Microencapsulation

ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY

Recent Volumes in this Series

Volume 662
OXYGEN TRANSPORT TO TISSUE XXXI
Edited by Duane F. Bruley and Eiji Takahasi

Volume 663
STRUCTURE AND FUNCTION OF THE NEURAL CELL ADHESION MOLECULE NCAM
Edited by Vladimir Berezin

Volume 664
RETINAL DEGENERATIVE DISEASES
Edited by Robert E. Anderson, Joe G. Hollyfield, and Matthew M. LaVail

Volume 665
FORKHEAD TRANSCRIPTION FACTORS
Edited by Kenneth Maiese

Volume 666
PATHOGEN-DERIVED IMMUNOMODULATORY MOLECULES
Edited by Padraic G. Fallon

Volume 667
LIPID A IN CANCER THERAPY
Edited by Jean-François Jeannin

Volume 668
SUPERMEN1
Edited by Katalin Balogh and Attila Patocs

Volume 669
NEW FRONTIERS IN RESPIRATORY CONTROL
Edited by Ikuo Homma and Hiroshi Onimaru

Volume 670
THERAPEUTIC APPLICATIONS OF CELL MICROENCAPSULATION
Edited by José Luis Pedraz and Gorka Orive

Therapeutic Applications of Cell Microencapsulation

Edited by

José Luis Pedraz, PhD
Laboratory of Pharmacy and Pharmaceutical Technology
University of the Basque Country, Vitoria-Gasteiz, Spain

Gorka Orive, PhD
Laboratory of Pharmacy and Pharmaceutical Technology
University of the Basque Country, Vitoria-Gasteiz, Spain

Springer Science+Business Media, LLC

Landes Bioscience

Springer Science+Business Media, LLC
Landes Bioscience

Printed in the USA.

Springer Science+Business Media, LLC, 233 Spring Street, New York, New York 10013, USA
http://www.springer.com

Please address all inquiries to the publishers:
Landes Bioscience, 1002 West Avenue, Austin, Texas 78701, USA
Phone: 512/ 637 6050; FAX: 512/ 637 6079
http://www.landesbioscience.com

The chapters in this book are available in the Madame Curie Bioscience Database.
http://www.landesbioscience.com/curie

Therapeutic Applications of Cell Microencapsulation, edited by José Luis Pedraz and Gorka Orive. Landes Bioscience / Springer Science+Business Media, LLC dual imprint / Springer series: Advances in Experimental Medicine and Biology.

ISBN: 978-1-4419-5785-6

Library of Congress Cataloging-in-Publication Data

Therapeutic applications of cell microencapsulation / edited by José Luis Pedraz, Gorka Orive.
p. ; cm. -- (Advances in experimental medicine and biology ; v. 670)
Includes bibliographical references and index.
ISBN 978-1-4419-5785-6
1. Animal cell biotechnology. 2. Microencapsulation. I. Pedraz, José Luis. II. Orive, Gorka. III. Series: Advances in experimental medicine and biology, v. 670. 0065-2598 ;
[DNLM: 1. Drug Compounding--methods. 2. Cells, Immobilized. 3. Drug Delivery Systems--methods. QV 778 T398 2010]
TP248.27.A53T54 2010
610.28--dc22

2009046493

DEDICATION

Gorka Orive dedicates the present book to his parents Araceli and Ramón, his wife Raquel and his brother Ibon.

José Luis Pedraz dedicates this book to his parents José Juan and Luisa, his wife Angela and his children Diana and Carlos.

FOREWORD

The advancement of science is ever more contingent upon the interaction of experts with different yet complementary sets of expertise. This is a natural consequence of the vast amount of scientific information being gathered every day that exceeds the ability of any one scientist to acquire. As an illustration of the frantic pace of scientific discovery, no single molecular biologist was able to keep up with all the available knowledge in the field by the 1980s, a mere two decades after its inception. This challenge is even more acute in the case of scientific fields at the interface of different and seemingly distant areas of study. Amidst these, the field of cell encapsulation brings together an array of diverse disciplines such as molecular biology and biopolymers, gene therapy and inorganic membranes, stem cell biology and physicochemistry, immunology and nanotechnology. Clearly, such range of topics is too broad for any individual scientist to cover with sufficient depth. The field is experiencing such a remarkable rate of growth that regular updates are necessary to keep abreast of the current knowledge. This book is aimed at providing the reader with a detailed and up-to-date account of the state-of-the-art in the field of cell encapsulation.

At the core of this technology, there is an interaction of physicochemical and biological elements forming three distinct layers of complexity. First, the chemistry of the biopolymer dictates the degree of protein adsorption, vascularization, toxicity and biocompatibility of the microcapsules. Advances in biopolymer science are providing solutions to overcome existing challenges and to improve microcapsules as delivery vehicles. Second, the choice of cells, and more precisely the plethora of metabolites they secrete, and how they interact with the polymer and the host, are key in determining the immune response elicited by the host to implanted microcapsules. Adequate cell viability is crucial to achieve long-term therapeutic delivery. Finally, most microcapsule applications are aimed at delivering a given therapeutic product that is missing or deficient in the host, and thus it is recognized as foreign by the immune system. In response to this insult, the host often generates a vigorous immune response that can seriously compromise the therapeutic delivery. This immune response is antigen-dependent, it is not necessarily identical for all transgenes, and thus must be considered independently for every medical application. Adding to this complexity, changes in one of the above-mentioned layers may also affect the other layers. As an

example, the choice of encapsulated cells may determine whether there is an immune response against the secretable transgene. Similarly, the purity of the polymer may influence the viability of the encapsulated cells. Therefore, it is imperative to consider and study the interaction of all three layers.

Type 1, or insulin dependent diabetes, was one of the first main applications of cell encapsulation. However, the initial promise of a treatment for this disease that imposes such a tremendous burden on both patients and health care system has not yet fully materialized. Despite these shortcomings, recent findings have provided us with a more detailed characterization of the immune responses against encapsulated islets, and in the process, new possibilities for more effective treatments are opening. Beyond diabetes, applications of cell encapsulation have been expanded to multiple human disorders. The initial exploration of intrathecal implantation of encapsulated cells into the CNS, have been followed by additional studies aimed at developing potential applications to very serious medical conditions, such as Parkinson, Alzheimer's, and stroke. Similarly, there are efforts to exploit cell encapsulation as a treatment for cancer, blood diseases and metabolic disorders. The maturity of the field is reflected in the various clinical trials that have explored the application of cell microencapsulation in medicine.

Recent developments in cell encapsulation have improved the outlook of this technology as a viable treatment for medical diseases. The knowledge resulting from the clinical trials, together with additional research on the basic physicochemical and biological characteristics of cell encapsulation will ultimately determine its feasibility.

Gonzalo Hortelano, PhD
Department of Pathology and Molecular Medicine
School of Biomedical Engineering
Faculty of Health Sciences
and
Faculty of Engineering
McMaster University
Hamilton, Ontario
Canada

PREFACE

The main objective of this book has been to analyze in depth and discuss the different aspects related to the design and elaboration of cell-enclosing microcapsules, even the regulatory features and clinical trials under development. These improvements will lead to progression in this therapeutic approach which may become one day closer to a realistic proposal for clinical application.

The advances in drug delivery technology have enabled a new era of drug discovery and development. In this regard, cell microencapsulation is a technology that opens new venues and possibilities to the administration of new active principles and may be the key to solve several issues related to the correct administration of new therapeutic agents to finally success in the clinical setting.

The editors believe that this technology may have important applicability not only in the field of drug delivery (to treat diseases such as cancer, neurodegenerative disorders, metabolic diseases etc.) but also in cellular therapy and tissue regeneration among others.

Due to the organization of the chapters, this book can be read at different levels and readers may analyze from basic aspects of encapsulation, biomaterials, clinical applications and regulatory and industrial issues of this technology. This book is useful for both graduate and PhD students in the pharmaceutical, engineering and biomedical fields. Nevertheless, we hope that this book is also useful to expert researchers who may find information and new ideas about the cell microencapsulation area.

The general aspects of the technology are analyzed in Chapter 1. The main issues related to the use and selection of biomaterials employed in this type of technology are discussed in Chapter 2. The importance of microcapsule size and the possibility of reducing it through different approaches are discussed in Chapter 3.

In order to succeed in the clinical setting, it is of great importance to take into consideration all the regulatory aspects that may determine the therapeutic applicability of this technology. These issues are discussed in Chapter 4.

In the following chapters the broad spectrum of pathologies that may be treated using cell microencapsulation technology are discussed. Chapter 5 presents the advances achieved in the treatment of diabetes using microencapsulated islets of

Langerhans. The use of microencapsulated cells for the treatment of diseases related to the haematopoyetic system are discussed in Chapter 6. Chapter 7 describes the latest advances achieved in the field of regenerative medicine and cell therapy using cell microencapsulation technology, which is nowadays gaining attention and being considered a very relevant and promising strategy for the area. Other pathologies discussed in the book (Chapter 8) deal with alterations and degenerative processes in the central nervous system and the approaches currently under study for the treatment of cancer (Chapter 9).

Chapters 10 and 11 examine the advances achieved in the field of inorganic nanoporous membranes and the aspects that will determine the future of this type of technology. Finally, Chapter 12 examines a very important issue related to the commercial applicability of cell microencapsulation.

Last but not least the editors would like to greatly thank all the participating authors for their dedicated contribution and help, which have been crucial to make the publication of this book possible.

José Luis Pedraz, PhD
Laboratory of Pharmacy and Pharmaceutical Technology
University of the Basque Country, Vitoria-Gasteiz, Spain

Gorka Orive, PhD
Laboratory of Pharmacy and Pharmaceutical Technology
University of the Basque Country, Vitoria-Gasteiz, Spain

ABOUT THE EDITORS...

JOSÉ LUIS PEDRAZ recieved the PhD degree in Pharmacy at the University of Salamanca, Spain. He is a professor of Pharmacy and Pharmaceutical Technology at the Faculty of Pharmacy at the Basque Country University. He is the cofounder and director of the Pharmaceutical Development Unit of the Basque Country. His interest is focused on the development and evaluation of pharmaceutical dosage forms (microcapsules, micro- and nanoparticles) for the administration of gene, proteins, peptides, vaccines and cells. Dr. Pedraz has published over 200 scientific articles and edited several book chapters on cell microencapsulation.

ABOUT THE EDITORS...

GORKA ORIVE received the PhD degree in Pharmacy and is currently an Assistant Professor of Pharmacy and Pharmaceutical Technology at the University of the Basque Country in Vitoria, Spain. He is the director of research publications and scientific coordinator in the field of oral implantology for Biotechnology Institute (BTI, Vitoria, Spain). His main interests are polymer-based cell therapy for long-term and controlled protein and growth factor delivery to different tissues including brain. He is also interested in the potential use of autologous platelets growth factors and fibrin scaffold for regenerative medicine. Dr. Orive has published more than 100 articles in national and international journals including *Nature Medicine, Nature Reviews Neurosciences, Molecular Therapy, Biomaterials, Trends in Pharmacological Sciences* among others and several book chapters focused on cell microencapsulation for therapeutic purposes and the use of plasma rich in growth factors in medicine.

PARTICIPANTS

Anthony Atala
Department of Urology
Institute for Regenerative Medicine
Wake Forest University
Winston Salem, North Carolina
USA

Briannan Bintz
InCytu, Inc.
Providence, Rhode Island
USA

Thomas Ming Swi Chang
Artificial Cells and Organs Research Centre
Departments of Physiology, Medicine and Biomedical Engineering
McGill University
Montreal, Quebec
Canada

Tejal Desai
UCSF/UCB Joint Graduate Group in Bioengineering
University of California, San Francisco
University of California, Berkeley
and
Department of Bioengineering and Therapeutic Sciences
Department of Physiology
University of California
San Francisco, California
USA

Dwaine F. Emerich
InCytu, Inc.
Providence, Rhode Island
USA

Marijke M. Faas
Department of Pathology and Laboratory Medicine
Section of Immunoendocrinology
University Hospital of Groningen
Groningen
The Netherlands

Walter H. Gunzburg
Institute of Virology
University of Veterinary Medicine
Vienna
Austria

Rosa Mª Hernández
Laboratory of Pharmacy and Pharmaceutical Technology
University of the Basque Country
Vitoria-Gasteiz
Spain

Gonzalo Hortelano
Department of Pathology and Molecular Medicine
School of Biomedical Engineering
Faculty of Health Sciences
and
Faculty of Engineering
McMaster University
Hamilton, Ontario
Canada

Koei Kawakami
Department of Chemical Engineering
Kyushu University
Fukuoka-City, Fukuoka
Japan

Grace J. Lim
Department of Urology
Institute for Regenerative Medicine
Wake Forest University
Winston Salem, North Carolina
USA

Zun Chang Liu
Artificial Cells and Organs Research Centre
Departments of Physiology, Medicine and Biomedical Engineering
McGill University
Montreal, Quebec
Canada

Stephan M. Meier
Düsseldorf
Germany
Email: s.m.meier@web.de

Adam Mendelsohn
UCSF/UCB Joint Graduate Group in Bioengineering
University of California, San Francisco
University of California, Berkeley
Califonia
USA

Ainhoa Murua
Laboratory of Pharmacy and Pharmaceutical Technology
University of the Basque Country
Vitoria-Gasteiz
Spain

Gorka Orive
Laboratory of Pharmacy and Pharmaceutical Technology
University of the Basque Country
Vitoria-Gasteiz
Spain

José Luis Pedraz
Laboratory of Pharmacy and Pharmaceutical Technology
University of the Basque Country
Vitoria-Gasteiz
Spain

Shinji Sakai
Department of Chemical Engineering
Kyushu University
Fukuoka-City, Fukuoka
Japan

Brian Salmons
Austrianova Singapore Pte Ltd.
Singapore

Edorta Santos
Laboratory of Pharmacy and Pharmaceutical Technology
University of the Basque Country
Vitoria, Gasteiz
Spain

Milica Spasojevic
Department of Pathology and Laboratory Medicine
Section of Immunoendocrinology
University Hospital of Groningen
Groningen
The Netherlands

Christopher G. Thanos
InCytu, Inc.
Providence, Rhode Island
USA

Paul de Vos
Department of Pathology and Laboratory Medicine
Section of Immunoendocrinology
University Hospital of Groningen
Groningen
The Netherlands

Mark Van Dyke
Department of Urology
Institute for Regenerative Medicine
Wake Forest University
Winston Salem, North Carolina
USA

J. van Zanten
Department of PLG Medical Biology
University Medical Center Groningen
University of Groningen
Groningen
The Netherlands

Jon Zarate
Laboratory of Pharmacy
and Pharmaceutical Technology
University of the Basque Country
Vitoria, Gasteiz
Spain

Shirin Zare
Department of Urology
Institute for Regenerative Medicine
Wake Forest University
Winston Salem, North Carolina
USA

CONTENTS

1. HIGHLIGHTS AND TRENDS IN CELL ENCAPSULATION 1

Gorka Orive and José Luis Pedraz

Abstract 1
Introduction 1
Pivotal Issues for the Progress in the Field 2
Therapeutic Applications of Cell Encapsulation Technology 3
Conclusion 4

2. BIOMATERIALS IN CELL MICROENCAPSULATION 5

Edorta Santos, Jon Zarate, Gorka Orive, Rosa Mª Hernández and José Luis Pedraz

Abstract 5
Introduction 5
Alginate 6
Other Polymers and Type of Biomaterials 14
Conclusion 16

3. DEVELOPMENT OF SUBSIEVE-SIZE CAPSULES AND APPLICATION TO CELL THERAPY 22

Shinji Sakai and Koei Kawakami

Abstract 22
Introduction 22
Narrow Dispersed Subsieve-Size Capsule Production Via the Jetting Process 23
Effect of Preparation Process on Mammalian Cells 26
Effect of Reduction in Microcapsule Diameter 27
Conclusion 28

4. REGULATORY CONSIDERATIONS IN APPLICATION OF ENCAPSULATED CELL THERAPIES 31

J. van Zanten and Paul de Vos

Abstract 31
Introduction 31
Background 32
Good Manufacturing Practice 32
Cell-Based Therapies 35
Conclusion 37

5. TREATMENT OF DIABETES WITH ENCAPSULATED ISLETS 38

Paul de Vos, Milica Spasojevic and Marijke M. Faas

Abstract 38
Introduction 38
Concepts of Encapsulation 39
Intravascular Designs 39
Extravascular Macrocapsules 41
Host Responses and Macroencapsulation 42
Extravascular Microcapsules 42
Biocompatibility and Microcapsule Composition 44
Biology of Encapsulated Cells 45
Conclusion 46

6. EPO DELIVERY BY GENETICALLY ENGINEERED C_2C_{12} MYOBLASTS IMMOBILIZED IN MICROCAPSULES 54

Ainhoa Murua, Gorka Orive, Rosa M[a] Hernández and José Luis Pedraz

Abstract 54
Introduction 54
Therapeutic Applications Beyond Erythropoiesis 55
Novel Erythropoiesis Stimulating Strategies: Potential New Treatments for Anemia 55
Cell Encapsulation Technology as an Alternative to Frequent Dosing Schemes 57
Conclusion 63

7. ARTIFICIAL CELL MICROENCAPSULATED STEM CELLS IN REGENERATIVE MEDICINE, TISSUE ENGINEERING AND CELL THERAPY 68

Zun Chang Liu and Thomas Ming Swi Chang

Abstract 68
Introduction 68
Cell Encapsulation 69

Adult Stem Cells and Their Plasticity **69**
Tissue Engineering of Bone Marrow Stem Cells **70**
Coencapsulation of Bone Marrow Stem Cells with Hepatoyctes to Enhance Hepatocytes Viability and Function **71**
Therapeutic Effect of Encapsulated Bone Marrow Stem Cells on the Liver Failure Model **73**
Conclusion **74**

8. MICROENCAPSULATED CHOROID PLEXUS EPITHELIAL CELL TRANSPLANTS FOR REPAIR OF THE BRAIN **80**

Christopher G. Thanos, Briannan Bintz and Dwaine F. Emerich

Abstract **80**
Introduction **80**
Basic Structure and Function of the Choroid Plexus **80**
The Central Role of the Choroid Plexus in Brain Development **82**
The Choroid Plexus in Aging **83**
Choroid Plexus and Neurodegeneration: Alzheimer's Disease (AD) as an Example **84**
Harnessing the Choroid Plexus for Transplantation Therapy: Preliminary Studies **84**
Immunoisolation within Alginate Microcapsules Enables the Use of Xenogeneic Choroid Plexus Transplants **85**
Characterization of Alginate and Encapsulated Choroidal Epithelial Cells **85**
Encapsulated Xenogeneic Choroid Plexus Transplants in Animal Models of Stroke **86**
Encapsulated Xenogeneic Choroid Plexus Transplants in a Rat Model of Huntington's Disease **87**
In Vitro and In Vivo Determinations of the Effect of Age on CP Function **88**
Encapsulated Xenogeneic Choroid Plexus Transplants in a Monkey Model of Huntington's Disease **89**
Conclusion **89**

9. THERAPEUTIC APPLICATION OF CELL MICROENCAPSULATION IN CANCER **92**

Brian Salmons and Walter H. Gunzburg

Abstract **92**
Introduction **92**
Preclinical Studies of Treatments with Therapeutic Products Produced from Encapsulated Cells **93**
Clinical Trials of Cancer Treatment Using Encapsulated Cells to Target Chemotherapy **98**
Combination Therapies—The Way for the Future? **100**
Retrovirus Vector Production from Encapsulated Cells **100**
Conclusion **102**

10. INORGANIC NANOPOROUS MEMBRANES FOR IMMUNOISOLATED CELL-BASED DRUG DELIVERY.... 104

Adam Mendelsohn and Tejal Desai

Abstract.... 104
Introduction.... 104
Cell-Based Drug Delivery.... 105
Immunosuppressed Cell Transplantation.... 106
Immunoisolated Cell-Based Drug Delivery.... 106
Inorganic Nanoporous Membranes.... 111
Conclusion.... 122

11. CELL MICROENCAPSULATION.... 126

Grace J. Lim, Shirin Zare, Mark Van Dyke and Anthony Atala

Abstract.... 126
Introduction.... 126
Why Is Microencapsulation Necessary?.... 126
Materials for Cell Microencapsulation.... 128
Geometry of Capsules Matters?.... 129
Clinical Impact of Microencapsulation Technology.... 132
Challenges in Cell Microencapsulation.... 133
Conclusion.... 134

12. COMMERCIAL APPLICABILITY OF CELL MICROANCAPSULATION: A REVIEW OF INTELLECTUAL PROPERTY RIGHTS.... 137

Stephan M. Meier

Abstract.... 137
Introduction.... 137
Retrieval of the Data Base.... 138
The Teaching of Bibliographic Data.... 138
More Detailed Discussion of Relevant Prior Art.... 142
Conclusion.... 142

INDEX.... 145

ACKNOWLEDGEMENTS

Gorka Orive would like to express his sincere gratitude to the research group in cell encapsulation at the Faculty of Pharmacy (Vitoria, Spain) for their help and unfaltering support.