MRS
MATERIALS RESEARCH SOCIETY
SYMPOSIUM PROCEEDINGS
Volume 550

Biomedical Materials—Drug Delivery, Implants and Tissue Engineering

EDITORS
Thomas Neenan
Michele Marcolongo
Robert F. Valentini

MATERIALS RESEARCH SOCIETY
SYMPOSIUM PROCEEDINGS VOLUME 550

Biomedical Materials—Drug Delivery, Implants and Tissue Engineering

Symposium held November 30–December 1, 1998, Boston, Massachusetts, U.S.A.

EDITORS:

Thomas Neenan
GelTex Pharmaceuticals, Inc.
Waltham, Massachusetts, U.S.A.

Michele Marcolongo
Drexel University
Philadelphia, Pennsylvania, U.S.A.

Robert F. Valentini
Brown University
Providence, Rhode Island, U.S.A.

MRS
Materials Research Society
Warrendale, Pennsylvania

Single article reprints from this publication are available through
University Microfilms Inc., 300 North Zeeb Road, Ann Arbor, Michigan 48106

CODEN: MRSPDH

Published by:

Materials Research Society
506 Keystone Drive
Warrendale, PA 15086
Telephone (724) 779-3003
Fax (724) 779-8313
Web site: http://www.mrs.org/

Library of Congress Cataloging in Publication Data

Biomedical materials—drug delivery, implants, and tissue engineering : symposium held November 30–December 1, 1998, Boston, Massachusetts, U.S.A. / editors, Thomas Neenan, Michele Marcolongo, Robert F. Valentini
p.cm.—(Materials Research Society symposium proceedings, ISSN 0272-9172 ; v. 550)
Includes bibliographical references and index.
ISBN 1-55899-456-4
1. Biomedical materials—Congresses. 2. Polymeric drug delivery systems—Congresses. 3. Biomedical engineering—Congresses. 4. Animal cell biotechnology—Congresses. I. Neenan, Thomas II. Marcolongo, Michele III. Valentini, Robert F. IV. Materials Research Society symposium proceedings ; v. 550
[DNLM: 1. Biomedical Engineering–methods—Congresses. 2. Drug Delivery Systems—Congresses. 3. Polymers—Congresses. 4. Prostheses and Implants—Congresses. 5. Tissue Transplantation—Congresses. QT 36 B6155 1999]
R857.M3B579 1999 99-25874
610'.28—dc21 CIP
DNLM/DLC for Library of Congress

Manufactured in the United States of America

Biomedical Materials—Drug Delivery, Implants and Tissue Engineering

CONTENTS

*Invited Paper

PART II: MUSCULOSKELETAL TISSUE ENGINEERING

*Invited Paper

*Invited Paper

*Invited Paper

PART VI: ORTHOPEDIC BEARING SURFACES AND NOVEL COATINGS

*Invited Paper

PREFACE

The continual growth and increasing sophistication of biomaterials industries has been driven in large part by advances in the basic sciences of the materials involved. Indeed, advances in understanding biological systems at the molecular level have quickly been exploited by materials scientists to develop more sophisticated approaches to therapeutics and diagnostics. The interdisciplinarity and breadth of the biomaterials field necessitates the close cooperation of scientists in many different fields, including materials science, chemistry, biology, engineering, and medicine.

The 1998 MRS Fall Meeting brought together researchers in many of these converging fields in the form of three symposia: "Polymeric Materials—Drugs, Delivery, and Devices," "Tissue Engineering," and "Advanced Materials, Coatings and Biological Cues for Medical Implants." Over 100 papers and posters from 20 countries were presented.

This proceedings volume brings together many of the oral and poster presentations that were given at these symposia, and is divided into six sections that approximate the symposia sessions. Lively discussions after each paper and during the poster sessions helped in the process of stimulating dialogue between participants from various disciplines. The only regret voiced frequently during the two days was frustration on the part of audience members who were forced, because of concurrent scheduling, to chose between talks of equal interest.

We hope that this volume provides a snapshot of the vigor and diversity of the biomaterials field at this time, and trust that the papers presented here stimulate further discussion and research in what will continue to be a vital area of discovery and development.

Thomas Neenan
Michele Marcolongo
Robert F. Valentini

February 1999

ACKNOWLEDGMENTS

The success of these three symposia, and the publication of this proceedings volume, is due to the efforts of many people to whom we are grateful. We wish to acknowledge the efforts of our co-organizers Elliot Chaikof (Emory University), Elizabeth Chen (Chen Consulting, Inc.), Achim Goepferich (University of Regensburg), Cato Laurencin (Drexel University), Grace Picciolo (Food and Drug Administration), John Ranieri (Sulzer Innotec Carbomed), Jeff Schryver (Smith & Nephew), and Kathryn Uhrich (Rutgers University). A note of thanks is extended to all of the speakers, poster presenters, and authors whose contributions comprise the body of this effort. We thank the MRS staff and the meeting chairs whose patience and efforts made our tasks much easier. We also gratefully acknowledge the generous financial support received from the following organizations; their contributions have helped make these symposia a success:

GelTex Pharmaceuticals, Inc.
Johnson & Johnson Professional, Inc.
New Jersey Center for Biomaterials & Medical Devices
Reprogenesis
Smith & Nephew Research, Ltd.
Sulzer Innotec Carbomedics
Telios Pharmaceuticals, Inc.

MATERIALS RESEARCH SOCIETY SYMPOSIUM PROCEEDINGS

Volume 507— Amorphous and Microcrystalline Silicon Technology—1998, R. Schropp, H.M. Branz, M. Hack, I. Shimizu, S. Wagner, 1999, ISBN: 1-55899-413-0
Volume 508— Flat-Panel Display Materials—1998, G. Parsons, C-C. Tsai, T.S. Fahlen, C. Seager, 1998, ISBN: 1-55899-414-9
Volume 509— Materials Issues in Vacuum Microelectronics, W. Zhu, L.S. Pan, T.E. Felter, C. Holland, 1998, ISBN: 1-55899-415-7
Volume 510— Defect and Impurity Engineered Semiconductors and Devices II, S. Ashok, J. Chevallier, K. Sumino, B.L. Sopori, W. Götz, 1998, ISBN: 1-55899-416-5
Volume 511— Low-Dielectric Constant Materials IV, C. Chiang, P.S. Ho, T-M. Lu, J.T. Wetzel, 1998, ISBN: 1-55899-417-3
Volume 512— Wide-Bandgap Semiconductors for High Power, High Frequency and High Temperature, S. DenBaars, J. Palmour, M.S. Shur, M. Spencer, 1998, ISBN: 1-55899-418-1
Volume 513— Hydrogen in Semiconductors and Metals, N.H. Nickel, W.B. Jackson, R.C. Bowman, R.G. Leisure, 1998, ISBN: 1-55899-419-X
Volume 514— Advanced Interconnects and Contact Materials and Processes for Future Integrated Circuits, S.P. Murarka, M. Eizenberg, D.B. Fraser, R. Madar, R. Tung, 1998, ISBN: 1-55899-420-3
Volume 515— Electronic Packaging Materials Science X, D.J. Belton, M. Gaynes, E.G. Jacobs, R. Pearson, T. Wu, 1998, ISBN: 1-55899-421-1
Volume 516— Materials Reliability in Microelectronics VIII, J.C. Bravman, T.N. Marieb, J.R. Lloyd, M.A. Korhonen, 1998, ISBN: 1-55899-422-X
Volume 517— High-Density Magnetic Recording and Integrated Magneto-Optics: Materials and Devices, J. Bain, M. Levy, J. Lorenzo, T. Nolan, Y. Okamura, K. Rubin, B. Stadler, R. Wolfe, 1998, ISBN: 1-55899-423-8
Volume 518— Microelectromechanical Structures for Materials Research, S. Brown, J. Gilbert, H. Guckel, R. Howe, G. Johnston, P. Krulevitch, C. Muhlstein, 1998, ISBN: 1-55899-424-6
Volume 519— Organic/Inorganic Hybrid Materials, R.M. Laine, C. Sanchez, C.J. Brinker, E. Giannelis, 1998, ISBN: 1-55899-425-4
Volume 520— Nanostructured Powders and Their Industrial Application, G. Beaucage, J.E. Mark, G.T. Burns, D-W. Hua, 1998, ISBN: 1-55899-426-2
Volume 521— Porous and Cellular Materials for Structural Applications, D.S. Schwartz, D.S. Shih, A.G. Evans, H.N.G. Wadley, 1998, ISBN: 1-55899-427-0
Volume 522— Fundamentals of Nanoindentation and Nanotribology, N.R. Moody, W.W. Gerberich, N. Burnham, S.P. Baker, 1998, ISBN: 1-55899-428-9
Volume 523— Electron Microscopy of Semiconducting Materials and ULSI Devices, C. Hayzelden, C. Hetherington, F. Ross, 1998, ISBN: 1-55899-429-7
Volume 524— Applications of Synchrotron Radiation Techniques to Materials Science IV, S.M. Mini, S.R. Stock, D.L. Perry, L.J. Terminello, 1998, ISBN: 1-55899-430-0
Volume 525— Rapid Thermal and Integrated Processing VII, M.C. Öztürk, F. Roozeboom, P.J. Timans, S.H. Pas, 1998, ISBN: 1-55899-431-9
Volume 526— Advances in Laser Ablation of Materials, R.K. Singh, D.H. Lowndes, D.B. Chrisey, E. Fogarassy, J. Narayan, 1998, ISBN: 1-55899-432-7
Volume 527— Diffusion Mechanisms in Crystalline Materials, Y. Mishin, G. Vogl, N. Cowern, R. Catlow, D. Farkas, 1998, ISBN: 1-55899-433-5
Volume 528— Mechanisms and Principles of Epitaxial Growth in Metallic Systems, L.T. Wille, C.P. Burmester, K. Terakura, G. Comsa, E.D. Williams, 1998, ISBN: 1-55899-434-3
Volume 529— Computational and Mathematical Models of Microstructural Evolution, J.W. Bullard, L-Q. Chen, R.K. Kalia, A.M. Stoneham, 1998, ISBN: 1-55899-435-1
Volume 530— Biomaterials Regulating Cell Function and Tissue Development, R.C. Thomson, D.J. Mooney, K.E. Healy, Y. Ikada, A.G. Mikos, 1998, ISBN: 1-55899-436-X
Volume 531— Reliability of Photonics Materials and Structures, E. Suhir, M. Fukuda, C.R. Kurkjian, 1998, ISBN: 1-55899-437-8

MATERIALS RESEARCH SOCIETY SYMPOSIUM PROCEEDINGS

Volume 532— Silicon Front-End Technology—Materials Processing and Modelling, N.E.B. Cowern, D.C. Jacobson, P.B. Griffin, P.A. Packan, R.P. Webb, 1998, ISBN: 1-55899-438-6
Volume 533— Epitaxy and Applications of Si-Based Heterostructures, E.A. Fitzgerald, D.C. Houghton, P.M. Mooney, 1998, ISBN: 1-55899-439-4
Volume 535— III-V and IV-IV Materials and Processing Challenges for Highly Integrated Microelectonics and Optoelectronics, S.A. Ringel, E.A. Fitzgerald, I. Adesida, D. Houghton, 1999, ISBN: 1-55899-441-6
Volume 536— Microcrystalline and Nanocrystalline Semiconductors—1998, L.T. Canham, M.J. Sailor, K. Tanaka, C-C. Tsai, 1999, ISBN: 1-55899-442-4
Volume 537— GaN and Related Alloys, S.J. Pearton, C. Kuo, T. Uenoyama, A.F. Wright, 1999, ISBN: 1-55899-443-2
Volume 538— Multiscale Modelling of Materials, V.V. Bulatov, T. Diaz de la Rubia, R. Phillips, E. Kaxiras, N. Ghoniem, 1999, ISBN: 1-55899-444-0
Volume 539— Fracture and Ductile vs. Brittle Behavior—Theory, Modelling and Experiment, G.E. Beltz, R.L. Blumberg Selinger, K-S. Kim, M.P. Marder, 1999, ISBN: 1-55899-445-9
Volume 540— Microstructural Processes in Irradiated Materials, S.J. Zinkle, G. Lucas, R. Ewing, J. Williams, 1999, ISBN: 1-55899-446-7
Volume 541— Ferroelectric Thin Films VII, R.E. Jones, R.W. Schwartz, S. Summerfelt, I.K. Yoo, 1999, ISBN: 1-55899-447-5
Volume 542— Solid Freeform and Additive Fabrication, D. Dimos, S.C. Danforth, M.J. Cima, 1999, ISBN: 1-55899-448-3
Volume 543— Dynamics in Small Confining Systems IV, J.M. Drake, G.S. Grest, J. Klafter, R. Kopelman, 1999, ISBN: 1-55899-449-1
Volume 544— Plasma Deposition and Treatment of Polymers, W.W. Lee, R. d'Agostino, M.R. Wertheimer, B.D. Ratner, 1999, ISBN: 1-55899-450-5
Volume 545— Thermoelectric Materials 1998—The Next Generation Materials for Small-Scale Refrigeration and Power Generation Applications, T.M. Tritt, M.G. Kanatzidis, G.D. Mahan, H.B. Lyon, Jr., 1999, ISBN: 1-55899-451-3
Volume 546— Materials Science of Microelectromechanical Systems (MEMS) Devices, A.H. Heuer, S.J. Jacobs, 1999, ISBN: 1-55899-452-1
Volume 547— Solid-State Chemistry of Inorganic Materials II, S.M. Kauzlarich, E.M. McCarron III, A.W. Sleight, H-C. zur Loye, 1999, ISBN: 1-55899-453-X
Volume 548— Solid-State Ionics V, G-A. Nazri, C. Julien, A. Rougier, 1999, ISBN: 1-55899-454-8
Volume 549— Advanced Catalytic Materials—1998, P.W. Lednor, D.A. Nagaki, L.T. Thompson, 1999, ISBN: 1-55899-455-6
Volume 550— Biomedical Materials—Drug Delivery, Implants and Tissue Engineering, T. Neenan, M. Marcolongo, R.F. Valentini, 1999, ISBN: 1-55899-456-4
Volume 551— Materials in Space—Science, Technology and Exploration, A.F. Hepp, J.M. Prahl, T.G. Keith, S.G. Bailey, J.R. Fowler, 1999, ISBN: 1-55899-457-2
Volume 552— High-Temperature Ordered Intermetallic Alloys VIII, E.P. George, M. Yamaguchi, M.J. Mills, 1999, ISBN: 1-55899-458-0
Volume 553— Quasicrystals, J-M. Dubois, P.A. Thiel, A-P. Tsai, K. Urban, 1999, ISBN: 1-55899-459-9
Volume 554— Bulk Metallic Glasses, W.L. Johnson, C.T. Liu, A. Inoue, 1999, ISBN: 1-55899-460-2
Volume 555— Properties and Processing of Vapor-Deposited Coatings, M. Pickering, B.W. Sheldon, W.Y. Lee, R.N. Johnson, 1999, ISBN: 1-55899-461-0
Volume 556— Scientific Basis for Nuclear Waste Management XXII, D.J. Wronkiewicz, J.H. Lee, 1999, ISBN: 1-55899-462-9

Prior Materials Research Society Symposium Proceedings available by contacting Materials Research Society

Part I

Polymeric Drugs and Delivery

THREE GENERATIONS OF BILE ACID SEQUESTRANTS

W. HARRY MANDEVILLE, WILLIAM BRAUNLIN, PRADEEP DHAL, AMY GUO, CHAD HUVAL, KAREN MILLER, JOHN PETERSEN, STEVEN POLOMOSCANIK, DAVID ROSENBAUM, ROBERT SACCHIERO, JAMES WARD AND S. RANDALL HOLMES-FARLEY, GelTex Pharmaceuticals, 9 Fourth Ave., Waltham, MA 02451

ABSTRACT

Cholestyramine, the first bile acid sequestrant to be marketed, has been in use for over 20 years. Despite its low potency, requiring 16-24 g of polymer to achieve 20% LDL cholesterol reduction in hypercholesterolemic individuals, only one other sequestrant, colestipol, has come to market in the ensuing period. GelTex Pharmaceuticals has been involved for over six years in the discovery and development of new, more potent polymeric sequestrants. Two binding mechanisms are presented – one that operates via an aggregate binding structure and one that is effective via a defined site binding structure. These two binding mechanisms are compared and contrasted through bile acid binding isotherms. The best of these new sequestrants bind bile acids through a combination of hydrophobicity and ion exchange. Optimization and balancing of each of these interactions led us to more potent materials. The first of these, colesevelam hydrochloride is expected to be three to four times more potent than cholestyramine. A third generation product is still in research at GelTex. With another twofold increase in potency possible, single tablet therapy may become a reality.

INTRODUCTION

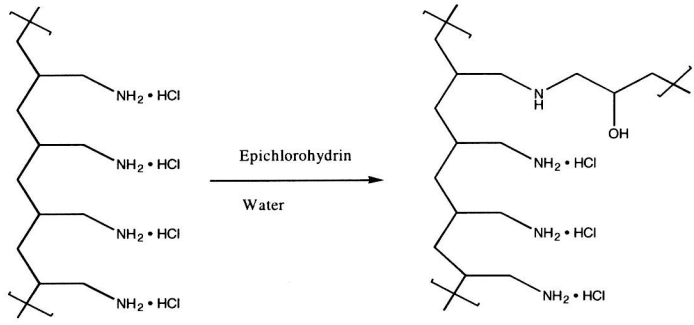
Elevated plasma total and LDL cholesterol (LDL_c) levels, hypertriglyceridemia, and a low HDL cholesterol (HDL_c) level are major risk factors for coronary artery disease (CAD). However, the majority of the individuals at risk require only a modest (20-30%) reduction in LDL_c to reach levels recommended by the National Cholesterol Education Program (NCEP) [1]. The reduction of elevated cholesterol levels is one of the most common therapeutic treatments for patients worldwide. The treatment regime of first choice is invariably dietary modification, but it has been shown to be of limited efficacy in the majority of patients [2]. One of the mechanisms for cholesterol reduction in hypercholesterolemic individuals is sequestration of bile acids. The sequestrants have a good safety record over a 30-year period, but large doses make compliance problematic. A more potent sequestrant, one that will reduce cholesterol with small doses such that tablet formulations are feasible, has been the object of many quests by several companies.

The concept of control of cholesterol through removal of bile acids was brought to reality by the introduction of cholestyramine, sold under the brand name Questran® by Bristol Laboratories (now Bristol Myers Squibb). Cholestyramine, first used in the treatment of hypercholesterolemia in 1959[1] was introduced in the early 1970's and since then the search for a better bile acid sequestrant has continued unabated. This search is documented in a review by Stedronsky[2]. The literature, both open and patent, describing "new" bile acid sequestrants is voluminous. Invariably, these new sequestrants have shown very high *in vitro* activity, and many have also claimed very high *in vivo* activity, but none have emerged as the replacement to cholestyramine.

Mat. Res. Soc. Symp. Proc. Vol. 550 © 1999 Materials Research Society

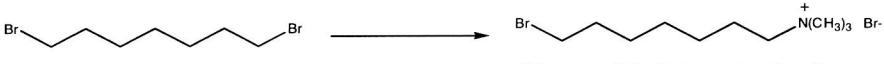
This paper will compare the two commercial sequestrants, cholestyramine and colestipol with a new sequestrant currently in phase III human clinical trials, colesevelam hydrochloride, and two experimental sequestrants that are candidates for human clinical development.

Experimental Section.



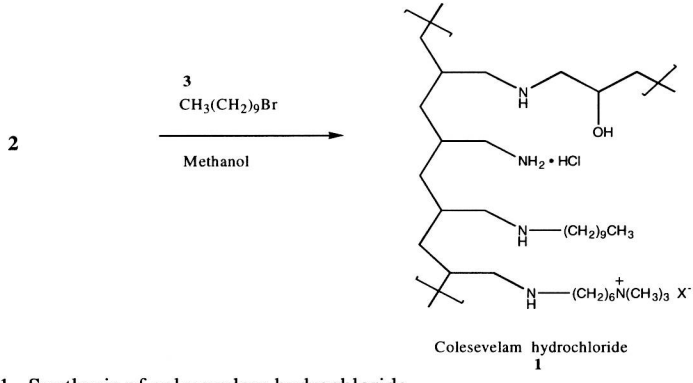
Polyallylamine

Cross-linked Polyallylamine
2



1,6-Dibromohexane

6-Bromohexyltrimethylammonium bromide
3



Colesevelam hydrochloride
1

Scheme 1. Synthesis of colesevelam hydrochloride

Materials. - Cholestyramine, cholyl glycine, sodium salt and glycochenodeoxy-cholic acid, sodium salt were purchased from Sigma Chemical Co. Polyallylamine was purchased from Nitto Boseki, Ltd., Japan. Epichlorohydrin, 1-bromodecane, 1,6-dibromohexane and trimethylamine were purchased from Aldrich Chemical Co.

Synthesis of cross-linked polyallylamine hydrochloride, **2**. Poly(allylamine hydrochloride) (2136.1 g of 50% aqueous solution, 11.42 equiv.) was dissolved in 3200 mL of deionized water