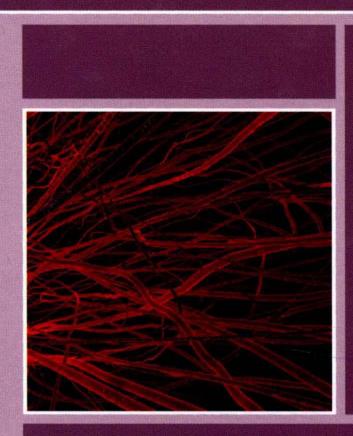
WOODHEAD PUBLISHING SERIES IN BIOMATERIALS



Nanofiber Composites for Biomedical Applications

Edited by
Murugan Ramalingam and Seeram Ramakrishna

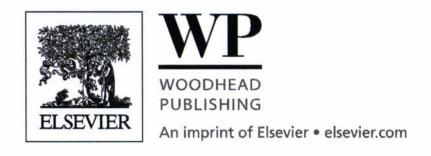


Woodhead Publishing Series in Biomaterials

Nanofiber Composites for Biomedical Applications

Edited by

Murugan Ramalingam Seeram Ramakrishna



Woodhead Publishing is an imprint of Elsevier
The Officers' Mess Business Centre, Royston Road, Duxford, CB22 4QH, United Kingdom
50 Hampshire Street, 5th Floor, Cambridge, MA 02139, United States
The Boulevard, Langford Lane, Kidlington, OX5 1GB, United Kingdom

Copyright © 2017 Elsevier Ltd. All rights reserved.

No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, or any information storage and retrieval system, without permission in writing from the publisher. Details on how to seek permission, further information about the Publisher's permissions policies and our arrangements with organizations such as the Copyright Clearance Center and the Copyright Licensing Agency, can be found at our website: www.elsevier.com/permissions.

This book and the individual contributions contained in it are protected under copyright by the Publisher(other than as may be noted herein).

Notice

Knowledge and best practice in this field are constantly changing. As new research and experience broaden our understanding, changes in research methods, professional practices, or medical treatment may become necessary.

Practitioners and researchers must always rely on their own experience and knowledge in evaluating and using any information, methods, compounds, or experiments described herein. In using such information or methods they should be mindful of their own safety and the safety of others, including parties for whom they have a professional responsibility.

To the fullest extent of the law, neither the Publisher nor the authors, contributors, or editors, assume any liability for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein.

ISBN 978-0-08-100173-8 (print) ISBN 978-0-08-100208-7 (online)

British Library Cataloguing-in-Publication Data

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

Library of Congress Cataloging-in-Publication Data

A catalog record for this book is available from the Library of Congress

For information on all Woodhead Publishing publications visit our website at https://www.elsevier.com





Working together to grow libraries in developing countries

www.elsevier.com • www.bookaid.org

Publisher: Matthew Deans Acquisition Editor: Gwen Jones

Editorial Project Manager: Tessa De Roo Production Project Manager: Omer Mukthar

Designer: Mark Rogers

Typeset by MPS Limited, Chennai, India

Nanofiber Composites for Biomedical Applications

Related Titles

Novel Fire Retardant Polymers and Composite Materials
(ISBN 978-0-08-100977-2)

Handbook of Advances in Braided Composite Materials: Theory, Production,
Testing and Applications
(ISBN 978-0-08-100369-5)

Recent Advances in Smart Self-Healing Polymers and Composites
(ISBN 978-1-78242-280-8)

The transfer of the

List of contributors

- S. Ahadian Tohoku University, Sendai, Japan
- L. Almeida University of Minho, Braga, Portugal
- J. Amit Kumar VIT University, Vellore, Tamil Nadu, India
- R. Asokamani VIT University, Vellore, Tamil Nadu, India
- S. Bairagi Singapore Eye Research Institute, Singapore, Singapore
- A. Baji Singapore University of Technology and Design (SUTD), Singapore, Singapore
- A. Barade VIT University, Vellore, Tamil Nadu, India
- J.P. Beier Friedrich-Alexander-University of Erlangen-Nürnberg, Bavaria, Germany
- A. Bhatt Vellore Institute of Technology, Vellore, Tamil Nadu, India
- **A.R. Boccaccini** University of Erlangen-Nuremberg, Erlangen, Germany
- A. Cai Friedrich-Alexander-University of Erlangen-Nürnberg, Bavaria, Germany
- C. Dhand Singapore Eye Research Institute, Singapore, Singapore
- N. Dwivedi National University of Singapore, Singapore, Singapore
- H. EI-Hamshary King Saud University, Riyadh, Saudi Arabia
- **T. Fukunishi** Nationwide Children's Hospital, Columbus, OH, United States
- C. Gandhimathi Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, Singapore
- M. Geetha VIT University, Vellore, Tamil Nadu, India
- **R.E. Horch** Friedrich-Alexander-University of Erlangen-Nürnberg, Bavaria, Germany

M. Lakshmi priya Centre for Stem Cell Research (CSCR), Vellore, Tamil Nadu, India

- **R.** Lakshminarayanan Singapore Eye Research Institute, Singapore, Singapore; Duke-NUS SRP Neuroscience and Behavioral Disorders, Singapore, Singapore
- M. Leena Karunya University, Coimbatore, Tamil Nadu, India
- L. Liverani University of Erlangen-Nuremberg, Erlangen, Germany
- Y.-W. Mai The University of Sydney, Sydney, NSW, Australia
- X. Mo Donghua University, Shanghai, China

xii

- S. Mohanty National Institute of Science Education and Research, HBNI, Jatni, Odisha, India
- **P. Muthukumaran** Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, Singapore
- **L.B. Naves** University of Minho, Braga, Portugal; CAPES Foundation, Ministry of Education of Brazil, Brasília, Brazil; National University of Singapore, Singapore, Singapore
- R. Obregón Tohoku University, Sendai, Japan
- R. Pasricha National Centre for Biological Sciences-TIFR, Bangalore, India
- A. Polini Radboud University Medical Center, Nijmegen, The Netherlands
- L. Rajamani Singapore Eye Research Institute-Singapore, Singapore, Singapore
- **S. Ramakrishna** National University of Singapore, Singapore, Singapore; Jinan University, Guangzhou, China
- M. Ramalingam Centre for Stem Cell Research (CSCR), Vellore, Tamil Nadu, India; Tohoku University, Sendai, Japan
- J. Ramón-Azcón Institute for Bioengineering of Catalonia (IBEC), Barcelona, Spain; CIBER de Bioingenieria, Biomateriales y Nanomedicina (CIBER-BBN), Barcelona, Spain
- D. Rana Centre for Stem Cell Research (CSCR), Vellore, Tamil Nadu, India
- G. Ratheesh National University of Singapore, Singapore, Singapore

List of contributors xiii

- J.A. Roether University of Erlangen-Nuremberg, Erlangen, Germany
- D. Sachdev National Institute of Food Technology Entrepeneurship and Management, Sonepat, India
- G. Salazar University of Texas Health Science Center, Houston, TX, United States
- T. Shinoka Nationwide Children's Hospital, Columbus, OH, United States
- T. Shoji Nationwide Children's Hospital, Columbus, OH, United States
- **D.K. Srinivasan** Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, Singapore
- H. Sriram Singapore Eye Research Institute, Singapore, Singapore
- B. Sun Donghua University, Shanghai, China
- T. Wu Donghua University, Shanghai, China
- F. Yang Radboud University Medical Center, Nijmegen, The Netherlands

Biographies



Murugan Ramalingam, PhD, FNS, FIoN, FRSC is a professor at the Centre for Stem Cell Research (a unit of the Institute for Stem Cell Biology and Regenerative Medicine, Bengaluru), Christian Medical College Campus, India. Concurrently he is an adjunct professor at the Tohoku University, Japan. Prior to joining the CSCR, he worked as Associate Professor of Biomaterials and Tissue Engineering at the Institut National de la Santé et de la Recherche Médicale, Faculté de Chirurgie Dentaire, Université de Strasbourg (France) and at the WPI Advanced Institute for Materials Research (Japan) as assistant professor. He has also worked at the National Institute

of Standards and Technology (NIST) and the National Institutes of Health (NIH), under the U.S. National Academies Associateship program. He received his PhD in Biomaterials from the University of Madras. He has also undergone training in Ethical and Policy issues on Stem Cells from Harvard University (United States), and in Operations Management from the University of Illinois at Chicago (United States). His current research interests focus on the development of multiphase biomedical materials, through conventional to nanotechnology to biomimetic approaches, microfabrication, cell patterning, stem cell differentiation, tissue engineering, and drug delivery. He is the author of over 275 publications, including peer-reviewed journal papers, conference proceedings, book chapters, authored books, edited books, and patents relevant to biomaterials, stem cells, and tissue engineering. His current h-index is 30 with ~6500 citations. He also serves as a board member of several international scientific and research committees in various public and private bodies and grant reviewer of various international funding agencies. He serves on the editorial boards of multiple biomaterials, stem cells and tissue engineering related journals, including as the Editor-in-Chief of the Journal of Biomaterials and Tissue Engineering, the Journal of Bionanoscience, and the Stem Cell Research and Therapy. He is a recipient of several prestigious fellowships and awards, including CSIR Fellowship (India), SMF Fellowship (Singapore), NRC National Academies Fellowship (United States), Nationale Professeur des Universités (France), Fellow of Institute of Nanotechnology (United Kingdom), and Fellow of Royal Society of Chemistry (United Kingdom).

Biographies



Professor Seeram Ramakrishna, FREng, FBSE is the Director of Center for Nanofibers & Nanotechnology, and a leader of Future of Manufacturing at the National University of Singapore (NUS). He is a Highly Cited Researcher in Materials Science (www.highlycited.com). He is among the World's Most Influential Scientific Minds (Thomson Reuters). He authored 1000 articles which attracted ~57,000 citations and ~110 h-index. His innovations have been translated into products. He is an editor of Current Opinion in Biomedical Engineering. He delivered over 200 plenary and keynote lectures around the world including a special lecture

at the Kavli Symposium on Nanosciences and Nanotechnologies, Norway. He is a fellow of UK Royal Academy of Engineering (FREng); Biomaterials Science and Engineering (FBSE); American Association of the Advancement of Science (AAAS); and American Institute for Medical & Biological Engineering (AIMBE) He is a recipient of IFEES President award—Global Visionary; Chandra P Sharma Biomaterials Award; Nehru Fellowship; LKY Fellowship; NUS Outstanding Researcher Award; IES and ASEAN Outstanding Engineer Award. He received PhD from the University of Cambridge, United Kingdom, and the General Management Training from Harvard University, United States.

Preface

Nanofibers have found widespread application in the biomedical field. To advance the usage and functionality of nanofibers, the concept of nanofiber composites has been introduced. Nanofiber composites have been developed extremely rapidly during the last few years, owing to the unique functional properties with which they are endowed and the fact that they often tend to perform better than their individual components. The unique characteristics of nanofiber composites, along with their remarkable suitability for surface modification and excellent mechanical performance, makes possible their use in a wide range of biomedical applications. The main objective and the essence of this book is therefore to present the new developments and impacts of nanofiber composites in various biomedical applications.

This book consists of 20 chapters, which are grouped into 4 parts. Part I (chapter: Introduction to nanofiber composites) deals with an introduction to nanofiber composites. Part II (chapters: Ceramic nanofiber composites; Polymer nanofiber composites; Metallic nanofiber composites) describes the classification of nanofiber composites. Here, the nanofiber composites are classified into three types: ceramic, polymeric, and metallic nanofiber composites. Part III (chapters: Physicochemical characterization of nanofiber composites; Mechanical characterization of nanofiber composites; Biological characterization of nanofiber composites) deals with the properties of nanofiber composites, wherein physicochemical, mechanical, and biological properties are focused upon. Part IV (chapters: Polymer nanofiber composites in drug delivery; Nanofiber composites in biomolecular delivery; Nanofiber composites for gene delivery; Nanofiber composites in skin tissue engineering; Nanofiber composites in bone tissue engineering; Nanofiber composites in cartilage tissue engineering; Nanofiber composites in tendon tissue engineering; Nanofibers in skeletal muscle tissue engineering; Nanofiber composites in neural tissue engineering; Nanofiber composites in cardiac tissue engineering; Nanofiber composites in vascular tissue engineering; Nanofiber composites in blood vessel tissue engineering; Clinical/preclinical aspects of nanofiber composites) highlights the biomedical applications of nanofiber composites, wherein key applications of drug delivery, biomolecular delivery, gene delivery, tissue engineering, and regenerative medicine are discussed.

This fascinating book features contributions from very experienced authors who are leaders in their fields. We, the Editors, sincerely hope that the information in this book will be a valuable resource for a wide audience, including graduate students, researchers, professors, scientists, bioengineers, clinicians, and industrial experts working in the field of nanofiber composites, nanobiotechnology, biomaterials, stem cells, drug delivery, tissue engineering, and regenerative medicine.

Murugan Ramalingam Seeram Ramakrishna

Contents

List	t of co	ontributors	xi
Bio	graph	nies	XV
Pre	face		xvii
Pa	rt I	Introduction to nanofiber composites	1
1	Intr	oduction to nanofiber composites	3
1		Ramalingam and S. Ramakrishna	3
	1.1	Introduction	3
	1.2	Classification of nanofiber composites	5
	1.3	Properties of nanofiber composites	5
	1.4		6
	1.5		9
	1.6	Biomedical applications of nanofiber composites	10
	1.7	Clinical translational aspects of nanofiber composites	19
	1.8	Commercial aspects of nanofiber composites	20
	1.9	Concluding remarks	25
		erences	25
	- 1011		
Pa	rt II	Classification of nanofiber composites	31
2	Cer	amic nanofiber composites	33
		Lakshmi priya, D. Rana and M. Ramalingam	
	2.1	Introduction	33
	2.2	Types of ceramic nanofiber composite	34
	2.3		37
	2.4	The second secon	39
	2.5	Biomedical applications of ceramic nanofiber composite	46
	2.6	Concluding remarks	50
	Refe	erences	50
3	Poly	mer nanofiber composites	55
		Paji and YW. Mai	
	3.1		55
	3.2	Nanofiber composites using electrospinning	56
	3.3	Modified electrospinning setup for scaffold design	60
	3.4		65
	3.5	Application of nanofiber composites	68

v i		Contents

	3.6	Future perspectives of polymer nanofiber	73	
	Ack	nowledgments	74	
	Refe	erences	74	
4	Metallic nanofiber composites		79	
		Iohanty and G. Manivasagam		
	4.1		79	
		Technological aspect	81	
	4.3	Metallic nanofiber composite applications in bio-medical		
		and health care	87	
	4.4	Conclusions and future perspectives	91	
	Refe	erences	92	
Pa	rt III	Properties of nanofiber composites	95	
5	Phy	sicochemical characterization of nanofiber composites	97	
	A. P	Polini and F. Yang		
	5.1	Introduction	97	
	5.2	Physicochemical characterization at molecular level	100	
	5.3	Physicochemical characterization at surface level	104	
	5.4		108	
	5.5	Conclusion	111	
	Refe	erences	111	
6	Med	chanical characterization of nanofiber composites	117	
	M. (Geetha, R. Asokamani, J. Amit Kumar		
	and	M. Ramalingam		
	6.1	Introduction	117	
	6.2	Nanotechnology and biomedicine	119	
	6.3	Tissue engineering	122	
	6.4	Scaffolds for tissue engineering	124	
	6.5	Electrospinning	127	
	6.6	Mechanical properties of nanofibers: case studies	130	
	6.7	Conclusion and future direction	151	
	Ack	nowledgment	153	
	Ref	erences	153	
7	Biological characterization of nanofiber composites			
	R. Pasricha and D. Sachdev			
	7.1	Introduction	157	
	7.2	Morphological characterization of nano fibers	158	
	7.3	Biomedical applications implicated characterization	166	
	7.4	Cell nanofiber scaffold interactive characterization	176	
	7.5	Concluding remarks	189	
	Ref	erences	190	

vii

Par	t IV	Biomedical Applications of Nanofiber	
	mpos	• •	197
	•		
8	Nano	fiber composites in drug delivery	199
		nand, N. Dwivedi, H. Sriram, S. Bairagi, D. Rana,	
		kshminarayanan, M. Ramalingam and S. Ramakrishna	
	8.1	Introduction	199
	8.2	Implications of nanofiber-based DDS in health care	201
	8.3	Composite nanofibers for drug delivery	202
	8.4	Applications of composite nanofibers as DDS	214
	8.5	Future prospects	218
	8.6	Concluding remarks	219
	Refer	rences	219
9	Nano	fiber composites in biomolecular delivery	225
		ena, A. Barade, D. Rana, C. Dhand, S. Ramakrishna	
		1. Ramalingam	
	9.1	Introduction	225
	9.2	Importance of biomolecules in biomedical applications	227
	9.3	Composite nanofibers for biomolecular delivery	228
	9.4	Release strategy of biomolecules from composite nanofiber scaffolds	237
	9.5	Applications of composite nanofibers for biomolecular delivery	240
	9.6	Preclinical status	244
	9.7	Concluding remarks	244
	Refer	rences	245
10	Nano	ofiber composites in gene delivery	253
10		akshmi priya, D. Rana, A. Bhatt and M. Ramalingam	233
	10.1	Introduction	253
	10.2		255
	10.3		257
		Characterization techniques	259
		Classification	261
	10.6		264
	10.7	Current status	264
	10.8	Conclusion	269
		rences	269
11	NT.	Chan annual to the last the state of the sta	2==
11		ofiber composites in skin tissue engineering	275
	11.1	Vaves, L. Almeida and L. Rajamani Introduction	275
			275 275
	11.2 11.3	Skin morphology Skin disorders	
			276 281
	11.4		
	11.5	Types of skin grafts and skin substitutes	282

	11.6 11.7 11.8	Tissue engineering Composite Nanofibrous Mats Impact of nanofibers in skin regeneration process	283 289 294
	11.9	Conclusion	295
	Ackn	owledgment	296
	Refer	ences	296
12	Nano	fiber composites in bone tissue engineering	301
	L. Liv	verani, J.A. Roether and A.R. Boccaccini	
	12.1	Introduction	301
	12.2	Topic overview	303
	12.3	Rationale for the selection of the inorganic phase for bone	
		tissue engineering applications	305
	12.4	Electrospinning and its integration with other scaffold	
		fabrication techniques for bone tissue engineering	306
	12.5		
		engineering	310
	12.6	Functionalized nanofiber composites	313
	12.7	In vivo applications of nanofiber composites for bone tissue	
		regeneration	314
	12.8	Conclusions	319
	Ackn	owledgements	319
		ences	319
13	Nano	fiber composites in cartilage tissue engineering	325
		ana, G. Ratheesh, S. Ramakrishna and M. Ramalingam	
	13.1	Introduction	325
	13.2	Microstructure of cartilage tissue	327
		Composite nanofiber for cartilage regeneration	330
	13.4		
		regeneration	336
	13.5	Future directions and perspectives	339
		ences	340
14	Nano	fiber composites in tendon tissue engineering	345
		o, T. Wu, B. Sun and H. EI-Hamshary	
	14.1	Introduction	345
	14.2	Different topological structure of nanofiber for tendon tissue	
		regeneration	346
	14.3	Development of three-dimensional scaffolds for tendon tissue	
		engineering	351
	14.4	Mechanical simulation of scaffold constructs for tendon tissue	ALTO AND ADDRESS OF THE PARTY O
	or white the	remodeling	356
	14.5	Growth factors and stem cells strategies incorporated	300
		with nanofibers in tendon tissue engineering	359

Contents

	14.6 Refer	Conclusion	365 365	
			369	
15	Nanofiber composites in skeletal muscle tissue engineering A. Cai, R.E. Horch and J.P. Beier			
	15.1	Introduction	369	
		Skeletal muscle anatomy	370	
	15.3	Tissue engineering of skeletal muscle	371	
	15.4	Three-dimensional matrices for skeletal muscle tissue engineering	375	
	15.5	Polymeric Materials for electrospun nanofibers	377	
	15.6	Mechanical and electrical stimulation of engineered skeletal		
		muscle	385	
	15.7	Vascularization and in vivo generation of 3D muscle constructs	386	
	15.8	Future aspects	387	
	15.9	Conclusion	389	
	Refer	ences	389	
16	Nano	fiber composites in neural tissue engineering	395	
		o, B. Sun, T. Wu and H. EI-Hamshary		
	16.1	Introduction	395	
	16.2	Composite nanofiber NGC	399	
	16.3	Nanofiber NGC with regular structure	400	
	16.4	Growth factor incorporated into nanofiber NTE scaffold	403	
		Conductive nanofiber NGC and electrical simulation for NTE	405	
		Conclusion	408	
	Refer	ences	409	
17	Nano	fiber composites in cardiac tissue engineering	411	
1 mm		andhimathi, P. Muthukumaran and D.K. Srinivasan		
	17.1	Introduction	411	
	17.2	Cardiac structure	412	
	17.3	Cardiac tissue remodeling	416	
		Cardiac tissue engineering	420	
	17.5	Fibrous scaffolds for building of cardiac tissue	421	
	17.6	Challenges and future trends in cardiac tissue engineering	441	
	17.7	Conclusion	443	
		owledgements	444	
	Refer	ences	444	
18	Nano	fiber composites in vascular tissue engineering	455	
		kunishi, T. Shoji and T. Shinoka		
	18.1	Introduction	455	
	18.2	Arterial TEVG	460	
	18.3	Electrospun nanofibers for arterial TEVG	462	
	18.4	Prevention of thrombosis, stenosis and calcification in		
		arterial TEVG	469	

x			Contents
	18.5	Current clinical status of TEVG	472
	18.6	Summary and perspectives for the future	473
	18.7	Conclusion	474
	Refer	rences	474
19	Nano	ofiber composites in blood vessel tissue engineering	483
		pregón, J. Ramón-Azcón and S. Ahadian	
	19.1	Introduction	483
	19.2	Natural/synthetic nanofiber composites	485
	19.3	Synthetic/synthetic nanofiber composites	496
	19.4	Conclusion and future perspectives	498
		rences	498
20	Clini	cal/preclinical aspects of nanofiber composites	507
	S. Ah	adian, R. Obregón, J. Ramón-Azcón, G. Salazar	
		M. Ramalingam	
	20.1	Introduction	507
	20.2	Status of clinically relevant biomaterials	508
	20.3	Clinical and preclinical applications of nanofiber	
		composite materials	509
	20.4	Conclusions and future remarks	518
	Ackn	owledgements	518
		rences	518
Ind	ev		529