

# The Immune Response to Implanted Materials and Devices

Bruna Corradetti  
Editor

# The Immune Response to Implanted Materials and Devices

The Impact of the Immune System  
on the Success of an Implant

 Springer

*Editor*

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# Foreword

In the powerfully emerging world of smart, or functional materials, I cannot imagine a class with greater potential impact on healthcare and societal benefits than biomaterials with an ability to modulate inflammatory response—precisely the subject focus of this exceptionally timely monograph edited by Dr. Bruna Corradetti.

All materials for use in healthcare elicit an inflammatory response, bar none; but exactly as inflammation can be a fundamental step in a healing process, or a formidable foe, if frustrated into a chronic manifestation, this biological response to a material interface can be essentially helpful, or profoundly detrimental. Materials technology, and our understanding of the many facets of inflammation, has finally reached a point of sufficient maturity and convergence, to make it possible, for biomaterials to be designed so as to elicit a beneficial, or at least a functionally neutral response from the biology with which they contact.

The downstream vision from this exciting vantage point potentially portends transformational breakthroughs in multiple domains of healthcare, ranging from lifelong orthopedic implants, to indwelling molecular sensors, brain-machine interfaces, regenerative biomaterial-cell combinations for applications in pancreatic and hepatic medicine, central and peripheral nervous system repair, T-cell transplantation and novel therapeutic systems. They comprise both, drug-delivery implants and systemic administration constructs, with the ability to preferentially concentrate at inflammatory sites, sense their biological surrounding, and respond accordingly to optimize therapeutic benefit and minimize adverse effects.

I express my enthusiastic support for Dr. Corradetti's efforts in realizing this extraordinary collection of contribution from world-leading experts, to place the convergence of inflammatory modulation and biomaterials on a firmer footing, for decades of scientific work in this nascent era. It has been an honor to serve in an

editorial advisory capacity for this volume, and a great added privilege to be able to do so in concert with two exceptionally distinguished scientists as Dr. Anthony Atala and Ali Khademhosseini. My gratitude goes to them and to the authors for their outstanding contributions.

With all of this, I wish you all happy readings and a pathway of rewarding research, enhanced by the contents of this important monograph.

Sincerely,  
*Dr. Mauro Ferrari*

# Preface

This textbook is intended to be a resource for biomaterial scientists and biomedical engineers, in both industry and academia, interested in the development of smart strategies able to exploit the self-healing properties of the body and achieve functional tissue restoration. Nowadays, many textbooks and journals discuss the broad spectra of material properties that can be customized for any specific applications but only few of them characterize in detail the host response, as the driving factor in determining the success of an implant.

Thanks to the perspectives offered by experts in the field of regenerative medicine, tissue engineering, surgery, immunology, nanomedicine, and transplantation, this textbook will guide the readers throughout the fascinating cascade of events activated in the body following the implant of biomaterials and devices. In Chap. 1 Dr. Badylak provides an overview of the host response to various categories of biomaterials for regenerative medicine applications, from a host-centric and a biomaterial-centric perspective. In Chap. 2 Dr. Anderson discusses the humoral and cellular events occurring at the implant site immediately following implantation. In Chap. 3, Dr. Giachelli presents the current understanding of macrophages, their functions in physiological processes and dysfunction in response to the foreign body, as well as approaches to guide them towards resolution of the foreign body-elicited inflammatory response. Dr. Dobrovolskaia proposes in Chap. 4 regulatory challenges, translational considerations, and literature case studies pertinent to the immunological safety of nanotechnology-based devices. Dr. Sant and Dr. Goldsmith provide a discussion about the effects of natural vs. synthetic biomaterials, as well as the role of the biomechanical environment on tissue fibrosis, in Chaps. 5 and 9, respectively. Highlights about the role of the biomechanical and physicochemical properties in osteo-immunomodulation and the effect of surface topographical modification on the cellular and molecular mechanisms associated with osseointegration are reported in Chaps. 6 and 8, by Dr. Xiao and Dr. Ivanovski. In Chap. 7, Dr. Li describes challenges and opportunities in targeting key elements of the innate immune system in favor of transplant survival. In Chap. 10, Dr. Sabek reviews possible solutions for the challenges encountered in the pancreatic islet transplantation field, while in Chap. 11 Dr. Tacke discusses current strategies to target macrophages

in liver diseases and cancer. Novel concepts of T-cell immunomodulation for their clinical translation are presented by Dr. Hildebrandt in Chap. 12 to allow the transfer of the knowledge gained to implanted materials and devices.

It has been a particular privilege for me to collaborate with each of the authors participating in this project, and I feel grateful for their inspired work and for the time they devoted to make this volume possible. I wish to express my public gratitude to Dr. Anthony Atala, Dr. Ali Khademhosseini, and Dr. Mauro Ferrari for serving as Editorial Advisors for this book, for their constant support, outstanding suggestions, and visionary ideas. It has been an honor working with you.

My greatest hope is that this book will stimulate further discussions and investigations on the powerful role of the host response in regenerative processes allowing for the development of cutting-edge approaches able to exploit it and achieve functional tissue healing.

Bruna Corradetti

Ancona, Italy

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# Abbreviations

ADA	Adenosine deaminase
aGvHD	Acute graft vs. host disease
ALP	Alkaline phosphatase
AMR	Antibody-mediated rejection
APC	Antigen-presenting cells
AST	Arginine stimulation test
ATMP	Advanced therapy medicinal product
BMI	Body mass index
BMP	Bone morphogenetic protein
CaP	Calcium phosphate direct deposition
CARPA	Complement activation related pseudoallergy
CaSR	Calcium sensing receptor
CCL	CC chemokine ligand
CDP	Common DC progenitor
cGvHD	Chronic graft vs. host disease
CID	Chemical inducer of dimerization
cMoP	Common myeloid progenitor
CSF	Colony-stimulating factor
CSFR	Colony-stimulating factor receptor
CXCL	Chemokine (C-X-C motif) ligand
CXCR	Chemokine receptor
DAF	Decay accelerating factor
DAMP	Damage-associated molecular pattern
DC	Dendritic cell
DDA	Degree of deacetylation
DKK-1	Dickkopf-1
DPP	Dipeptidyl peptidase
ECad	Epithelial cadherin
ECM	Extracellular matrix
EDRF	Endothelial-derived relaxing factor
EGF	Epidermal growth factor

egf- $\alpha$	Tumor necrosis factor
EPCs	Endothelial progenitor cells
ER	Endoplasmic reticulum
ETS	E26 transformation-specific
FACS	Fluorescence-activated cell sorting
FBC	Foreign body capsule
FBGCs	Foreign body giant cells
FBR	Foreign body reaction
FDA	Food and Drug Administration
FG	Fasting glucose
FGF	Fibroblast growth factor
FXIIA	Activated Hageman factor
GDSC	Glutaraldehyde cross-linked collagen
GlcN	D-Glucuronic and D-glucosamine
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GvHD	Graft vs. host disease
H1/H2	Histamine receptor
HA	Hyaluronic acid
HDSC	Hexamethylenediisocyanate
HETE	Hydroxyeicosatetraenoic acid
HIF	Hypoxia-inducible factors
HLA	Human leukocyte antigen
HMGB	High-mobility group box chromosomal protein
HRG	Histidine-rich glycoprotein
HSA	Human serum albumin
HSC	Hepatic stellate cells
HSCT	Hematopoietic stem cell transplantation
HUVECs	Human umbilical vein endothelial cells
IAT	Islet auto-transplantation
IBMIR	Instant blood mediated immune reaction
ICOS	Inducible costimulatory
IDE	Investigational device exemption
IFG	Impaired fasting glucose tolerance
IFN	Interferon
IGF	Insulin growth factor
IgG	Immunoglobulin G
IL	Interleukin
IL-R	Interleukin receptor
ILC	Innate lymphoid cells
IND	Investigational new drug
iNOS	Inducible nitric oxide synthase
IVGTT	Intravenous injection of glucose tolerance test
KC	Kupffer cells
KIR	Killer cell immunoglobulin-like receptors
KLF	Kruppel-like factor

LPS	Lipopolysaccharide
LRR	Leucine-rich repeat motifs
LTB <sub>4</sub>	Leukotriene B <sub>4</sub>
LVAD	Left ventricular assist devices
M1	Classically activated macrophages or pro-inflammatory macrophages
M2	Alternatively activated macrophages or anti-inflammatory/pro-wound healing macrophages
MCP-1	Monocyte chemotactic protein 1
M-CSF	Macrophage colony-stimulating factor
MDP	Monocyte-macrophage DC progenitor
MDSC	Myeloid-derived suppressor cells
MHC	Major histocompatibility complex
MIP	Macrophage inflammatory protein
miR	microRNA
MMP	Matrix metalloprotease
modSLA	Sandblasted hydrophilic nano-rough surface
MoMF	Monocyte-derived macrophage(s)
MPS	Mononuclear phagocyte system
MSCs	Mesenchymal stromal cells
MSFM	Memphis serum-free media
MWCNT	Multi-walled carbon nanotubes
NBD-PE	1,2-Dioleoyl-sn-glycero-3-phosphoethanolamine-N-(7-nitro-2-1,3-benzoxadiazol-4-yl)
NF- $\kappa$ B	Nuclear <i>factor</i> kappa
NGF	Neuronal growth factor
NK	Natural killer
NLR	NOD-like receptors
NO	Nitric oxide
OGTT	Oral glucose tolerance test
OPG	Osteoprotegerin
OSM	Oncostatin M
PAMAM	Polyamidoamine
PAMP	Pathogen-associated molecular patterns
PBMA	Poly(butylmethacrylate)
PCA	Procoagulant activity
PCBMA	Poly(carboxybetaine methacrylate)
PCL	Poly( $\epsilon$ -caprolactone)
PDGF	Platelet-derived growth factor
PDMS	Polydimethylsiloxane
PDO	Polydioxanone
PEG	Polyethylene glycol
PGA	Polyglycolide
PI/IRI	Proinsulin to immunoreactive insulin
PIBCA	Polyisobutyl
PIHCA	Polyisohexylcyanoacrylate

PLA	Poly lactide
PLGA	Poly(lactic-co-glycolic acid)
PLGA-PLL	Poly(lactic-co-glycolic acid)-poly-L-lysine
PMB	Poly(2-methacryloyloxyethyl phosphorylcholine(MPC)-co-n-butylmethacrylate(BMA)s)
PMNs	Polymorphonuclear leukocytes
POPC	1-Palmitoyl-2-oleoyl phosphatidylcholine
PPAR	Peroxisome proliferator-activated receptor
PRR	Pattern recognition receptor
PTFE	Polytetrafluoroethylene
PU	Polyurethane
PVA	Polyvinyl alcohol
PVA-SPION	Poly(vinyl alcohol)-coated superparamagnetic iron oxide nanoparticles
QD	Quantum dots
RANKL	Receptor activator of nuclear factor kappa-B ligand
RBC	Red blood cells (erythrocytes)
RES	Reticuloendothelial system
RGD	Arginine-glycine-aspartic acid
RLR	RIG-like receptors
ROS	Reactive oxygen species
SIBS	Poly(styrene-isobutylene-styrene) copolymer
SLA/Sr	Sandblasted micro-rough surface containing strontium
SLA	Sandblasted micro-rough surface
SOST	Sclerostin
SRBC	Sheep red blood cells
STZ	Streptozotocin
T1DM	Type 1 diabetes mellitus
TAM	Tumor-associated macrophages
T-cells	Thymocytes
TGF	Transforming growth factor
TIMP	Tissue inhibitor of metalloprotease
TLR	Toll-like receptors
TNF	Tumor necrosis factor
t-PA	Tissue-type plasminogen activator
T-regs	T-regulatory cells
VEGF	Vascular endothelial growth factor
VEGFR	VEGF receptor
VFH	Vinylidene fluoride-hexafluoropropylene copolymer
Zr-SLA & Zr-modSLA	Zirconium alloy SLA and modSLA surfaces