## Contents

### Part I  Introduction and Scientific Principles

1. From Hemoglobin Based Oxygen Carrier to Oxygen Therapeutics, Blood Substitutes, Nanomedicine and Artificial Cells ................................... 3  
   Thomas Ming Swi Chang

2. From the Atmosphere to the Mitochondrion:  
   The Oxygen Cascade ........................................... 27  
   George P. Biro

3. Biochemistry of Hemoglobin ............................... 55  
   Andrea Mozzarelli, Stefano Bruno and Luca Ronda

4. The Role of Blood and Plasma Viscosity in Restoring Oxygen Delivery Capacity ........................................... 75  
   Amy G. Tsai, Judith Martini, Beatriz Y. Salazar Vázquez, Pedro Cabrales, Seetharama A. Acharya and Marcos Intaglietta

### Part II  Hemorrhagic Shock and Current Treatments

5. Pathophysiology of Hemorrhagic Shock and Resuscitation  ...... 97  
   Fredric M. Pieracci and Walter L. Biffl

6. Allogeneic Blood Transfusion for Surgical and Traumatic Hemorrhage ........................................... 117  
   Mercy Kuriyan and Jeffrey L. Carson

7. Pre-Hospital Fluid Resuscitation in Civilian and Military Populations ........................................... 127  
   Robert M. Van Haren, Chad M. Thorson, Col Lorne H. Blackbourne and Kenneth G. Proctor
Part III  Current Issues of HBOCs and Regulatory Framework

8  NIH/FDA/DOD Interagency Working Group on Oxygen Therapeutics .................................................. 141
Phyllis Mitchell, Richard Weiskopf, Warren M. Zapol
and Oxygen Therapeutics Working Group

9  Regulatory Framework for Hemoglobin-Based Oxygen Carrier Trials .............................................. 149
Basil Golding

Part IV  Approaches to HBOCs

10 HBOCs from Chemical Modification of Hb .......................................................... 159
Ronald Kluger and Francine E. Lui

11 Design of Nonhypertensive Conjugated Hemoglobins as Novel Resuscitation Fluids ......................... 185
Seetharama A. Acharya, Marcos Intaglietta, Amy G. Tsai and Fantao Meng

12 Cellular-Type Hemoglobin-Based Oxygen Carriers to Mimic the Red Blood Cell Structure ................ 235
Hiromi Sakai

13 Recombinant Octameric Hemoglobins as Resuscitation Fluids in a Murine Model of Traumatic Brain Injury
   Plus Hemorrhagic Shock ............................................................................................................ 249
Xianren Wu, Nancy T. Ho, Tong-Jian Shen, Vincent Vagni,
David K. Shellington, Keri Janesko-Feldman, Tsuey Chyi S. Tam,
Ming F. Tam, Patrick M. Kochanek, Chien Ho
and Virgil Simplaceanu

14 Liposome-Encapsulated Hemoglobin as an Artificial Oxygen Carrier: Technological Features, Manufacturing and Issues for Practical Application .......................................................... 273
Shinichi Kaneda, Takanobu Ishizuka, Hiroshi Goto
and Hiroaki Kasukawa

15 Zero-Link Hemoglobin (OxyVita®): Impact of Molecular Design Characteristics on Pre-clinical Studies .......... 283
John P. Harrington and Hanna Wollocko
Polynitroxylated Pegylated Hemoglobin (PNPH): A Nanomedicine for Critical Care and Transfusion

Li Ma, Frances M. Thompson, Dong Wang and Carleton J. C. Hsia

ATP-Adenosine-GSH Crosslinked Hb, An Oxygen Carrier with Pharmacological Properties for Multiple Therapeutic Indications

Jan Simoni, Grace Simoni and John F. Moeller

Albumin-Heme Oxygen Carriers

Teruyuki Komatsu

Recombinant Human Hb-SOD Fusion Proteins

Marie Grey, Khuanpiroon Ratanasopa and Leif Bülow

In-Vitro Production of Functional RBCs from Hematopoietic Stem Cells

Eun Jung Baek and Hyun Ok Kim

Part V Potential Applications of HBOCs

Liposome-Encapsulated Hemoglobin: Potential Clinical Applications

Akira T. Kawaguchi, Chieko Murayama, Fumiaki Yoshiba, Hiroyuki Furuya, Mariko Yamano and Munetaka Haida

Biocompatibility of Hemoglobin Vesicles, a Cellular-Type Artificial Oxygen Carrier, on Blood Cells and Plasma Proteins In Vitro and In Vivo

Hiroshi Azuma, Mitsuhito Fujihara and Hiromi Sakai

Polymerized Human Placenta Hemoglobin: Organ Protective Effects and Alternative Clinical Uses

Tao Li, Chengmin Yang, Jin Liu, Jiaxin Liu and Wang Hong

Low Volume Resuscitation with HBOCs in Hemorrhagic Shock

P. S. Reynolds, R. W. Barbee and K. R. Ward

Ischemic Rescue with Hemoglobin-Based Oxygen Carriers

Raymond C. Koehler
Part VI Preclinical Evaluations of HBOCs

26 Pre-clinical Evaluation of Hemoglobin Based Oxygen Carriers: Animal Models and Biomarkers ........................................ 457
Paul W. Buehler and Felice D’Agnillo

27 The Hemoglobin-Based Oxygen Carrier, HBOC-201, as a Resuscitation Fluid for Traumatic Hemorrhagic Shock: The Naval Medical Research Center Experience .............. 475
Charles Auker, Paula Moon-Massat, Anke Scultetus, Richard McCarron and Daniel Freilich

28 Cellular-Type Hemoglobin-Based Oxygen Carrier as a Resuscitative Fluid for Hemorrhagic Shock: Acute and Long-Term Safety Evaluation Using Beagle Dogs .......... 501
Tatsuhiko Ikeda, Hirohisa Horinouchi, Yoraro Izumi, Hiromi Sakai and Koichi Kobayashi

Part VII HBOC Clinical Trials

29 Key Adverse Events in Recent HBOC Phase III Clinical Trials and Their Causal Relationship to Test HBOC’s. ............. 527
Colin F. Mackenzie

30 Some Critical Comments on the Major HBOC Clinical Trials . . . 543
George P. Biro

31 Compassionate Use Cases Treated with Hemoglobin-Based Oxygen Carriers .......................................................... 563
Paula Moon-Massat and Daniel Freilich

Part VIII HBOC-Mediated Adverse Effects

32 Acellular Hemoglobin-Based Oxygen Carrier Mediated Blood Pressure Elevation and Vasoconstriction: A Review of Proposed Mechanisms and Contributing Factors ............... 587
Hae Won Kim

33 HBOCs and Cardiac Integrity ........................................... 621
T. N. Estep
<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors/Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>34</td>
<td>Effects of Hemoglobin-Based Oxygen Carriers on Blood Coagulation</td>
<td>Jonathan S. Jahr, Molly Chung, Afsaneh Anvarhosseini and Hae Won Kim</td>
</tr>
<tr>
<td>35</td>
<td>Redox Activity of Cell-Free Hemoglobin: Implications for Vascular Oxidative Stress and Endothelial Dysfunction</td>
<td>Felice D’Agnillo</td>
</tr>
<tr>
<td>36</td>
<td>HBOC Interferences with Routine Clinical Laboratory Tests</td>
<td>Younes Smani</td>
</tr>
<tr>
<td>37</td>
<td>Vasoconstriction, Hypertension and Oxidative Toxicity are Regulated by Polymerized Hemoglobin Size</td>
<td>Brian M. Belcik and Andre F. Palmer</td>
</tr>
<tr>
<td>38</td>
<td>Acellular Hemoglobin-Based Oxygen Carrier Induced Vasoactivity: A Brief Review of Potential Pharmacologic Remedies</td>
<td>Hae Won Kim, Chi-Ming Hai and A. Gerson Greenburg</td>
</tr>
<tr>
<td></td>
<td><strong>Part IX</strong> A Call for Collaborative Research and Development</td>
<td></td>
</tr>
<tr>
<td>39</td>
<td>International Consortium for Development of Hemoglobin-Based Oxygen Carriers, Oxygen Therapeutics and Multifunctional Resuscitation Fluids—A White Paper</td>
<td>Hae Won Kim, Jonathan S Jahr, Andrea Mozzarelli and Hiromi Sakai</td>
</tr>
</tbody>
</table>
Hemoglobin-Based Oxygen Carriers as Red Cell Substitutes and Oxygen Therapeutics
Kim, H.W.; Greenburg, A.G. (Eds.)
2013, XXIII, 746 p. 130 illus., 77 illus. in color., Hardcover
ISBN: 978-3-642-40716-1