Platelets have attracted increasing interest among clinicians and basic scientists over recent years, and are now known to play a part in many physiological and pathological conditions. In fact, platelets are involved in diseases responsible for the majority of disability and death worldwide, including myocardial infarction, stroke, peripheral vascular disease, cancer, and many infections. Platelets are also studied as a model in many areas of neurobiology, pharmacology, biochemistry and molecular biology.

This timely reference provides a comprehensive, detailed, up-to-date resource for clinicians and researchers, covering the structure and function of platelets and their role in pharmacology, pathogenesis and therapeutics. It is organized into sections covering platelet physiology, laboratory and methodological issues, platelet involvement in disease, including hemostatic and non-hemostatic conditions, platelet pharmacology, and treatment in the clinic.

With contributions from leading authorities including some of the founders of modern platelet studies, this is the definitive reference and guide to the diagnosis and therapeutics of diseases involving platelets. Chapters are devised to provide a critical review of the most clinically relevant aspects of the subject, with extensive references and easy-to-read take-home messages. It will be an essential resource for biomedical scientists and clinicians in hematology, vascular medicine, cardiology, thrombosis and related disciplines.

Paolo Gresele is Associate Professor of Internal Medicine, Section of Internal and Cardiovascular Medicine, Department of Internal Medicine, University of Perugia, Italy

Clive Page is Professor of Pharmacology, Division of Pharmacology and Therapeutics and Director of the Sackler Institute of Pulmonary Pharmacology and Therapeutics, Guy's, King's and St Thomas' School of Biomedical Sciences, London

Valentin Fuster is Director of the Zena and Michael A. Wiener Cardiovascular Institute and the Richard Garlin, M.D./Heart Research Foundation Professor of Cardiology at the Mount Sinai Medical Center and School of Medicine, New York, New York

Jos Vermylen is Professor of Internal Medicine, Centre for Molecular and Vascular Biology, University of Leuven, Belgium
Platelets in Thrombotic and Non-thrombotic Disorders
Pathophysiology, Pharmacology and Therapeutics

Edited by
Paolo Gresele
Section of Internal and Cardiovascular Medicine
Department of Internal Medicine
University of Perugia, Italy

Clive P. Page
Sackler Institute of Pulmonary Pharmacology
King's College London, UK

Valentin Fuster
The Mount Sinai Medical Center and
School of Medicine
New York, USA

and

Jos Vermylen
Centre for Molecular and Vascular Biology
University of Leuven, Belgium
Contents

List of contributors ix
Editors’ preface xxi

PART I PHYSIOLOGY

1 History of platelets 3
   J. Fraser Mustard, Raelene L. Kinhough-Rathbone
   and Marian A. Packham

2 Production of platelets 25
   Arnaud Drouin and Elisabeth Cramer

3 Morphology and ultrastructure of platelets 41
   James G. White

4 Platelet heterogeneity: physiology and pathological consequences 70
   Anthony Mathur and John F. Martin

5 Platelet membrane proteins as adhesion receptors 80
   Yoshiaki Tomiyama, Masamichi Shiraga and
   Sanford J. Shattil

6 Dynamics of the platelet cytoskeleton 93
   Kurt L. Barkalow, Hervé Falet and John Hartwig

7 Platelet organelles 104
   Francine Rendu and Brigitte Brohard-Bohn

8 Platelet receptors for thrombin 113
   Lawrence F. Brass, Marina Molino, Peter J.
   O’Brien and Mark Kahn

9 Platelet receptors: ADP 127
   Christian Gachet and Jean-Pierre Cazenave

10 Platelet receptors: prostanoids 140
   Roberta Vezza and Garret A. FitzGerald
# Contents

11 Platelet receptors: collagen  
Pia R-M. Siljander and Richard W. Farndale  
158

12 Platelet receptors: von Willebrand factor  
Jerry Ware and Zaverio M. Ruggeri  
179

13 Platelet receptors: fibrinogen  
Edward F. Plow, Thomas A. Haas and Tatiana V. Byzova  
188

14 Platelet signalling: GTP-binding proteins  
Jan-Willem N. Akkerman  
204

15 Platelet phospholipases A$_2$  
Michael H. Gelb, Carine M. Mounier, Ying He, and Steve P. Watson  
221

16 Roles of phospholipase C and phospholipase D in receptor-mediated platelet activation  
Mauro Torti and Eduardo G. Lapetina  
238

17 Platelet signalling: calcium  
Juan A. Rosado and Stewart O. Sage  
260

18 Platelet signalling: protein kinase C  
Charles S. Abrams and Marcelo G. Kazanietz  
272

19 Platelet signalling: tyrosine kinases  
Sylviane Levy-Toledano  
281

20 Platelet signalling: cAMP and cGMP  
James L. Daniel, Barrie Ashby and Fabio M. Pulcinelli  
290

21 Platelet adhesion  
Philip G. de Groot and Jan J. Sixma  
304

22 The platelet shape change  
Adrian R.L. Gear and Renata K. Polanowska-Gabrowska  
319

23 Aggregation  
Marian A. Pacham, Margaret L. Rand and Raelene L. Kinlough-Rathbone  
338

24 Amplification loops: release reaction  
Marc E. Huyseraerts  
357

25 Amplification loops: thromboxane generation  
Paola Patrignani and Maria G. Sciulli  
369

26 Platelet procoagulant activities: the amplification loops between platelets and the plasmatic clotting system  
H. Coenraad Hemker  
381

27 Platelets and chemotaxis  
Stefania Moni and Paolo Gresele  
393

28 Platelet–leukocyte interactions relevant to vascular damage and thrombosis  
Chiara Cerletti, Virgilio Evangelista, Roberto Lorenzet and Giovanni de Gaetano  
412

29 Vascular control of platelet function  
Scott Willoughby and Joseph Loscalzo  
432

## PART II METHODOLOGY

30 In vitro assays for evaluating platelet function  
Perumal Thiagarajan and Kenneth K. Wu  
459

31 Monitoring antiplatelet therapy  
Dermot Cox and Desmond Fitzgerald  
471

32 Flow cytometric analysis of platelet function  
Alan D. Michelson, Marc R. Barnard, Lori A. Krueger, A.L. Frelinger III and Mark I. Furman  
485

33 Animal models of platelet-dependent thrombosis  
Paolo Golino and Francesco Loffredo  
499

## PART III PATHOLOGY

A Hemostasis

34 Hereditary thrombocytopenias  
Chris Van Geet, Kathleen Freson, Rita Devos and Jos Vermylen  
515

35 Thrombocytopenias due to bone marrow disorders  
Beng H. Chong and Colin Chesterman  
528

36 Immune-mediated thrombocytopenia  
Kathryn E. Webert and John G. Kelton  
542

37 Thrombocytopenia in childhood  
Cécile Kaplan, M. Dreyfus, V. Proulle and G. Tchernia  
556

38 alloimmune thrombocytopenia  
E. Anders Kolb and James B. Bussel  
569

39 Drug-induced and drug-dependent immune thrombocytopenias  
Andreas Greinacher, Petra Eichler and Norbet Lubenow  
584

40 Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome  
Miha Furlan  
610
<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Pages</th>
</tr>
</thead>
<tbody>
<tr>
<td>41</td>
<td>Thrombocytosis and thrombocythemia</td>
<td>623</td>
</tr>
<tr>
<td></td>
<td>Tiziano Barbui and Guido Finazzi</td>
<td></td>
</tr>
<tr>
<td>42</td>
<td>Platelet adhesive protein defect disorders</td>
<td>639</td>
</tr>
<tr>
<td></td>
<td>Kenneth J. Clemetson and Jeannine M. Clemetson</td>
<td></td>
</tr>
<tr>
<td>43</td>
<td>Congenital disorders of platelet secretion</td>
<td>655</td>
</tr>
<tr>
<td></td>
<td>Marco Cattaneo</td>
<td></td>
</tr>
<tr>
<td>44</td>
<td>Congenital platelet signal transduction defects</td>
<td>674</td>
</tr>
<tr>
<td></td>
<td>A. Koneti Rao</td>
<td></td>
</tr>
<tr>
<td>45</td>
<td>Acquired platelet function defects</td>
<td>689</td>
</tr>
<tr>
<td></td>
<td>Joel S. Bennett</td>
<td></td>
</tr>
<tr>
<td>46</td>
<td>Platelet storage and transfusion</td>
<td>707</td>
</tr>
<tr>
<td></td>
<td>Scott Murphy</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td><strong>Thrombosis</strong></td>
<td></td>
</tr>
<tr>
<td>47</td>
<td>Pathophysiology of arterial thrombosis</td>
<td>727</td>
</tr>
<tr>
<td></td>
<td>Lina Badimon, Juan-Jose Badimon and Valentin Fuster</td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>Platelets and atherosclerosis</td>
<td>738</td>
</tr>
<tr>
<td></td>
<td>Peter Verhamme and Paul Holvoet</td>
<td></td>
</tr>
<tr>
<td>49</td>
<td>Platelet involvement in venous thrombosis and pulmonary embolism</td>
<td>753</td>
</tr>
<tr>
<td></td>
<td>Andrew D. Blann and Gregory Y. H. Lip</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>Gene regulation of platelet function</td>
<td>760</td>
</tr>
<tr>
<td></td>
<td>Thomas J. Kunicki</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td><strong>Non-hemostatic disorders</strong></td>
<td></td>
</tr>
<tr>
<td>51</td>
<td>Platelets and bacterial infections</td>
<td>783</td>
</tr>
<tr>
<td></td>
<td>Mark C. Herzberg and Ke Gong</td>
<td></td>
</tr>
<tr>
<td>52</td>
<td>Interactions of viruses and platelets and the inactivation of viruses</td>
<td>807</td>
</tr>
<tr>
<td></td>
<td>in platelet concentrates prepared for transfusion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Laurence Corash</td>
<td></td>
</tr>
<tr>
<td>53</td>
<td>Platelets and parasites</td>
<td>815</td>
</tr>
<tr>
<td></td>
<td>Michel Joseph</td>
<td></td>
</tr>
<tr>
<td>54</td>
<td>Platelets and tumours</td>
<td>824</td>
</tr>
<tr>
<td></td>
<td>Maria Benedetta Donati and Virgilio Evangelista</td>
<td></td>
</tr>
<tr>
<td>55</td>
<td>Platelets and renal diseases</td>
<td>837</td>
</tr>
<tr>
<td></td>
<td>Paola Boccardo, Miriam Galbusera and Giuseppe Remuzzi</td>
<td></td>
</tr>
<tr>
<td>56</td>
<td>Platelets and allergic diseases</td>
<td>852</td>
</tr>
<tr>
<td></td>
<td>Simon Pitchford and Clive P. Page</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td><strong>Pharmacology</strong></td>
<td></td>
</tr>
<tr>
<td>57</td>
<td>Platelet interactions with other cells related to inflammatory</td>
<td>869</td>
</tr>
<tr>
<td></td>
<td>diseases</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patrice E. Pouhelle and Pierre Borgeat</td>
<td></td>
</tr>
<tr>
<td>58</td>
<td>Platelets and the preimplantation stage of embryo development</td>
<td>885</td>
</tr>
<tr>
<td></td>
<td>Christopher O’Neill</td>
<td></td>
</tr>
<tr>
<td>59</td>
<td>Platelets in psychiatric and neurological disorders</td>
<td>894</td>
</tr>
<tr>
<td></td>
<td>B. E. Leonard</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>Platelets in inflammatory bowel disease</td>
<td>907</td>
</tr>
<tr>
<td></td>
<td>Elizabeth Carty, David S. Rampton and Carole E. Collins</td>
<td></td>
</tr>
<tr>
<td>PART V</td>
<td><strong>Therapy</strong></td>
<td></td>
</tr>
<tr>
<td>61</td>
<td>Aspirin</td>
<td>919</td>
</tr>
<tr>
<td></td>
<td>Carlo Patrono</td>
<td></td>
</tr>
<tr>
<td>62</td>
<td>Pharmacology of ticlopidine and clopidogrel</td>
<td>929</td>
</tr>
<tr>
<td></td>
<td>Jean-Pierre Cazenave and Christian Gachet</td>
<td></td>
</tr>
<tr>
<td>63</td>
<td>Platelet membrane glycoprotein (GP) IIb–IIIa antagonists and acute</td>
<td>940</td>
</tr>
<tr>
<td></td>
<td>arterial thrombosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>David R. Phillips and Lisa Nannizzi-Alaimo</td>
<td></td>
</tr>
<tr>
<td>64</td>
<td>Other antiplatelet agents</td>
<td>955</td>
</tr>
<tr>
<td></td>
<td>Luigi Iuliano, Fausta Michelella and Francesco Violi</td>
<td></td>
</tr>
<tr>
<td>65</td>
<td>Pharmacogenetics as a new antiplatelet strategy</td>
<td>964</td>
</tr>
<tr>
<td></td>
<td>Giovanni de Gaetano, Chiara Cerletti and Licia Iacioviello</td>
<td></td>
</tr>
<tr>
<td>66</td>
<td>Cardiovascular gene therapy: implications for platelet vessel wall</td>
<td>978</td>
</tr>
<tr>
<td></td>
<td>interactions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pierre Zoldhelyi, Harold Eichstaedt, Thomas Jax, Janice M. McNatt,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Zhi Qiang Chen, Harris Rose and James T. Willerson</td>
<td></td>
</tr>
<tr>
<td>67</td>
<td>Pharmacological modulation of the inflammatory actions of platelets</td>
<td>991</td>
</tr>
<tr>
<td></td>
<td>Carla Cicala and Giuseppe Cirino</td>
<td></td>
</tr>
<tr>
<td>68</td>
<td>Design of trials to evaluate antiplatelet agents</td>
<td>1003</td>
</tr>
<tr>
<td></td>
<td>Shamir R. Mehta, John W. Eikelboom and Salim Yusuf</td>
<td></td>
</tr>
<tr>
<td>Page</td>
<td>Contents</td>
<td></td>
</tr>
<tr>
<td>------</td>
<td>----------</td>
<td></td>
</tr>
<tr>
<td>69</td>
<td>Antiplatelet therapy in cardiology 1013 Herbert D. Aronow and Eric J. Topol</td>
<td></td>
</tr>
<tr>
<td>70</td>
<td>Antiplatelet therapies in neurology 1040 Graeme J. Hankey</td>
<td></td>
</tr>
<tr>
<td>71</td>
<td>Antiplatelet treatment in peripheral vascular disease 1055 Raymond Verhaeghe</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Afterword 1063</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Platelets: a personal story 1063 Gustav V. R. Born</td>
<td></td>
</tr>
</tbody>
</table>

Index 1073

Colour plates between pages 170 and 171
Contributors

Charles S. Abrams
University of Pennsylvania
Basic Research Building II/III Room 912
421 Curie Blvd.
Philadelphia
PA 19104, USA

Jan-Willem N. Akkerman
Laboratory for Thrombosis and Haemostasis
Department of Haematology
University Medical Center Utrecht
Heldelberglaan 100
3584 CX Utrecht
The Netherlands

Herbert D. Aronow
Department of Cardiovascular Medicine
The Cleveland Clinic Foundation – Clinic Centre
9500 Euclid Avenue
Cleveland
Ohio, USA

Barrie Ashby
Department of Pharmacology and Sol Sherry Thrombosis
Research Center
Temple University Medical School Philadelphia
PA 19140, USA

Juan-Jose Badimon
Cardiovascular Institute
Mount Sinai School of Medicine
New York, USA
Jean-Pierre Cazenave
INSERM U.311
Etablissement Français du Sang-Alsace
10 rue Spielmann
BP 36
67065 Strasbourg Cedex, France

Chiara Cerletti
Department of Vascular Medicine and Pharmacology
Consorzio Mario Negri Sud
66030 Santa Maria Imbaro, Italy

Zhi Qiang Chen
Wafic Said Molecular Cardiology and Gene Therapy
Research Laboratory and Cullen Research Laboratory
Texas Heart Institute
University of Texas Medical School
Houston
Texas, USA

Colin Chesterman
Centre for Thrombosis and Vascular Research
University of New South Wales
Sydney
NSW, Australia

Beng H. Chong
University of New South Wales
WR Pitney Building
St. George Hospital
Belgrave Street
Kogarah, Sydney
NSW 2017, Australia

Carla Cicala
Department of Experimental Pharmacology
University of Naples Federico II
via D. Montesano 49
80131 Naples, Italy

Giuseppe Cirino
Department of Experimental Pharmacology
University of Naples Federico II
via D. Montesano 49
80131 Naples, Italy

Jeannine M. Clemetson
Theodor Kocker Institute
University of Berne
Freiestrasse 1
CH-3012 Berne, Switzerland

Kenneth J. Clemetson
Theodor Kocker Institute
University of Berne
Freiestrasse 1
CH-3012 Berne, Switzerland

Carole E. Collins
West Middlessex University Hospital
Iseleworth
Middlesex TW7 6AE UK

Laurence Corash
Cerus Corporation and Department of Laboratory Medicine
University of California
2411 Stanwell Drive
Concord
San Francisco
CA 94520, USA

Dermot Cox
Centre for Cardiovascular Science
Royal College of Surgeons
Dublin, Ireland

Elisabeth Cramer
INSERM U.474
Hôpital de Port Royal
123 Boulevard de Port-Royal
75014 Paris, France

James L. Daniel
Department of Pharmacology and Sol Sherry Thrombosis Research Center
Temple University Medical School Philadelphia
PA 19140, USA

Rita: De Vos
Morphology and Molecular Pathology
University Hospital Leuven, Belgium

Maria Benedetta Donati
Department of Vascular Medicine and Pharmacology
Istituto di Ricerche Farmacologiche Mario Negri
Consorzio Mario Negri Sud
66030 Santa Maria Imbaro, Italy
xii List of contributors

M. Dreyfus
Unité d’Immunologie Plaquettaire
INTS
6 rue A. Cabanel
75015 Paris, France

Guido Finazzi
Division of Hematology
Ospedali Riuniti
Largo Barozzi 1
24128 Bergamo, Italy

Arnaud Drouin
INSERM U.474
Hôpital de Port Royal
123 Boulevard de Port-Royal
75014 Paris, France

Desmond Fitzgerald
Centre for Cardiovascular Science
Royal College of Surgeons
Dublin, Ireland

Petra Eichler
Institute for Immunology and Transfusion Medicine
Ernst-Moritz-Arndt-University
Greifswald, Germany

Garret A. FitzGerald
Center for Experimental Therapeutics
University of Pennsylvania
421 Curie Boulevard
Philadelphia
PA 19104, USA

Harold Eichstadt
Wacik Said Molecular Cardiology and Gene Therapy
Research Laboratory and Cullen Research Laboratory
Texas Heart Institute
University of Texas Medical School
Houston
Texas, USA

A.L. Frelinger III
Center for Platelet Function Studies
University of Massachusetts Medical School
55 Lake Avenue North
Worcester
MA 01655, USA

John W. Eikelboom
Department of Haematology
Royal Perth Hospital
Perth, Australia

Kathleen Freson
Centre for Molecular and Vascular Biology
University Hospital Leuven, Belgium

Virgilio Evangelista
Department of Vascular Medicine and Pharmacology
Istituto di Ricerche Farmacologiche Mario Negri
Consorzio Mario Negri Sud
66030 Santa Maria Imbaro, Italy

Miha Furlan
Liebegeweg 7
CH-3006 Bern, Switzerland

Hervé Falet
Brigham & Women’s Hospital
Hematology Division
LMRC Building, Rm 301
221 Longwood Avenue
Boston
MA 02115, USA

Mark I. Furman
Center for Platelet Function Studies
University of Massachusetts Medical School
55 Lake Avenue North
Worcester
MA 01655, USA

Richard W. Farndale
University of Cambridge
Department of Biochemistry
Cardiovascular Biology Section
Building O
Downing Site
Cambridge CB2 1QW, UK

Valentin Fuster
The Mount Sinai Medical Center
Mount Sinai School of Medicine
Box 1030
One Gustave L. Levy Place
New York
NY 10029, USA
List of contributors xiii

Christian Gachet
INSM U.311
Etablissement Français du Sang Alsace
10 rue Spielmann
BP 36
67065 Strasbourg Cedex, France

Giovanni de Gaetano
Università Cattolica del Sacro Cuore
Centro di Ricerca e Formazione ad Alta Tecnologia nelle Scienze Biomediche
86100 Campobasso, Italy

Miriam Galbusera
Mario Negri Institute for Pharmacological Research
Via Gavazzeni 11
24125 Bergamo, Italy

Adrian R.L. Gear
Department of Biochemistry and Molecular Genetics
University of Virginia School of Medicine
Charlottesville
VA 22908, USA

Michael H. Gelb
Departments of Chemistry and Biochemistry
University of Washington
Seattle
Washington, USA

Paolo Golino
Division of Cardiology
University of Naples "Federico II"
via Sergio Pansini 5
80131 Naples, Italy

Ke Gong
Department of Preventive Sciences
School of Dentistry
University of Minnesota
17–164 Moos Tower
515 Delaware St.
S.E. Minneapolis
Minnesota 55455, USA

Andreas Greinacher
Institute for Immunology and Transfusion Medicine
Ernst-Moritz Arndt-University
Greifswald, Germany

Paolo Gresele
Department of Internal Medicine
Section of Internal and Cardiovascular Medicine
University of Perugia
Via E. Dal Pozzo
06126 Perugia, Italy

Philip G. de Groot
University Medical Center
Department of Haematology
Room G03.647
P.O. Box 8550
3508 GA Utrecht
The Netherlands

Thomas A. Haas
Joseph J. Jacobs Center for Thrombosis and Vascular Biology
Department of Molecular Cardiology
Cleveland Clinic Foundation
9500 Euclid Avenue
Cleveland
OH 44195, USA

Graeme J. Hankey
Stoke Unit
Royal Perth Hospital
Wellington Street
Perth
Western Australia 6001

John Hartwig
Brigham & Women’s Hospital
Hematology Division
LMRC Building, Rm 301
221 Longwood Avenue
Boston
MA 02115, USA

Ying Hefner
Departments of Chemistry and Biochemistry
University of Washington
Seattle
Washington, USA

H.C. Hemker
Synapse b.v. CARIM
PO Box 616
6200 MD Maastricht
The Netherlands
Mark C. Herzberg
Department of Preventive Sciences
School of Dentistry
University of Minnesota
17–164 Moos Tower
515 Delaware St.
S.E. Minneapolis
Minnesota 55455, USA

Paul Holvoet
Cardiovascular Research Unit of the Center for Experimental Surgery and Anesthesiology
KU Leuven
University of Leuven
Campus Gasthuisberg
O&N Herestraat 49
B-3000 Leuven, Belgium

Marc F. Hoyaerts
Center for Molecular and Vascular Biology
KU Leuven MCM group
Herestraat 49
B-3000 Leuven, Belgium

Marcos Hoylaerts
Center for Molecular and Vascular Biology
KU Leuven MCM group
Herestraat 49
B-3000 Leuven, Belgium

Licia Iacoviello
Department of Vascular Medicine and Pharmacology
Consorzio Mario Negri Sud
66030 Santa Maria Imbaro, Italy

Luigi Iuliano
University of Rome La Sapienza
Institute of Clinical Medicine 1
00185 Rome, Italy

Thomas Jax
Wafic Said Molecular Cardiology and Gene Therapy Research Laboratory and Cullen Research Laboratory
Texas Heart Institute
University of Texas Medical School
Houston
Texas, USA

Michel Joseph
INSERM IFR 17
Institut Pasteur de Lille, France

Mark Kahn
Department of Medicine
University of Pennsylvania
952 BRB II/III
421 Curie Blvd
Philadelphia
PA 19104-6069, USA

Cécile Kaplan
Unité d’Immunologie Plaquettaire
INTS
6 rue A. Cabanel
75015 Paris, France

Marcelo G. Kazanietz
University of Pennsylvania
Basic Research Building II/III Room 912
421 Curie Blvd.
Philadelphia
PA 19104, USA

John G. Kelton
Department of Medicine
Faculty of Health Sciences
McMaster University
Hamilton
Ontario, Canada

Raelene L. Kinlough-Rathbone
Department of Pathology and Molecular Medicine
McMaster University
Hamilton
Ontario, Canada

E. Anders Kolb
Cornell University Medical Center
New York Hospital, USA

Lori A. Krueger
Center for Platelet Function Studies
University of Massachusetts Medical School
55 Lake Avenue North
Worcester
MA 01655, USA

Thomas J. Kunicki
The Scripps Research Institute
10550 N. Torrey Pines Road
MEM-150
La Jolla
CA 92037, USA
List of contributors

Eduardo G. Lapetina
Cato Research Ltd.
200 Westpark Corporate Center
4364 South Alston Avenue
Durham
NC 27713–2280, USA

Brian Leonard
Pharmacology Department
National University of Ireland
Galway, Ireland

Sylviane Levy-Toledano
INSERM U.348
IFR Circulation Lariboisière
Hôpital Lariboisière
Paris, France

Gregory Y. H. Lip
Haemostasis, Thrombosis and Vascular Biology Unit
University Department of Medicine
City Hospital
Birmingham B18 7QH, UK

Francesco Loffredo
Division of Cardiology
University of Naples "Federico II"
via Sergio Pansini 5
80131 Naples, Italy

Roberto Lorenzetti
Department of Vascular Medicine and Pharmacology
Consorzio Mario Negri Sud
66030 Santa Maria Imbaro, Italy

Joseph Loscalzo
Whitaker Cardiovascular Institute
Evans Department of Medicine
Boston University School of Medicine
Boston
Massachusetts 02118–2393, USA

Norbet Lubenow
Institute for Immunology and Transfusion Medicine
Ernst-Moritz-Arndt-University
Greifswald, Germany

Janice M. McNatt
University of Texas Medical School
6431 Fannin
MSB 6.043
Houston
TX 77030, USA

John F. Martin
Centre for Cardiovascular Biology and Medicine
British Heart Foundation Laboratories
University College London, UK

Anthony Mathur
Centre for Cardiovascular Biology and Medicine
British Heart Foundation Laboratories
University College London, UK

Shamir R. Mehta
Division of Cardiology
Hamilton Health Sciences Corporation
McMaster University
Hamilton, Canada

Fausta Micheletta
University of Rome La Sapienza
Institute of Clinical Medicine 1
00185 Rome, Italy

Alan D. Michelson
Center for Platelet Function Studies
University of Massachusetts Medical School
55 Lake Avenue North
Worcester
MA 01655, USA

Marina Molino
Istituto di Ricerche Farmacologiche Mario Negri
Consorzio Mario Negri Sud
Santa Maria Imbaro, Italy

Stefania Momoi
Department of Internal Medicine
Section of Internal and Cardiovascular Medicine
University of Perugia
Via E. Dal Pozzo
06126 Perugia, Italy

Carine M. Mounier
Département de Biologie
Université de Cergy-Pontoise
95302 Cergy-Pontoise Cedex, France
List of contributors

Scott Murphy
American Red Cross Blood Services
Penn-Jersey Region
Philadelphia PA, USA

J. Fraser Mustard
The Founders' Network-CIAR
401 Richmond Street
Suite 281
Toronto
Ontario M5V 3A8, Canada

Lisa Nannizzi-Alaimo
COR Therapeutics, Inc.
256 East Grand Avenue
South San Francisco
CA 94080, USA

Peter J. O'Brien
Genaera Corp.
5110 Campus Drive
Plymouth Meeting, PA 19462, USA

Christopher O'Neill
Human Reproduction Unit
Department of Physiology
University of Sydney
Royal North Shore Hospital
St. Leonards
2065 NSW, Australia

Marian A. Packham
Department of Biochemistry
University of Toronto
Toronto
Ontario M5S 1A8, Canada

Clive P. Page
Department of Pharmacology
King's College London
5th floor
Hodgkin Building
Guy's Campus
London SE1 9RT, UK

Paola Patrignani
Department of Medicine and Aging
Division of Pharmacology
‘G. D'Annunzio’ University of Chieti
Via dei Vestini, 31
66013 Chieti, Italy

Carlo Patruno
Department of Pharmacology
University of Rome ‘La Sapienza’
Rome, Italy

David R. Phillips
COR Therapeutics, Inc.
256 East Grand Avenue
South San Francisco
CA 94080, USA

Simon Pitchford
Sackler Institute of Pulmonary Pharmacology
GKT School of Biomedical Sciences
Guy's Campus
King's College
London SE1 9RT, UK

Edward F. Plow
Joseph J. Jacobs Center for Thrombosis and Vascular Biology
Department of Molecular Cardiology
Cleveland Clinic Foundation
9500 Euclid Avenue
Cleveland
OH 44195, USA

Renata K. Polanowska-Grabowska
Department of Biochemistry and Molecular Genetics
University of Virginia School of Medicine
Charlottesville
VA 22908, USA

Patrice E. Poubelle
CRRI, Room T1–49
2705 Boulevard Laurier
Ste-Foy
Qc G1V 4G2, Canada

V. Prouillé
Unité d'Immunologie Plaquettaire
INTS
6 rue A. Cabanel
75015 Paris, France

Fabio M. Pulcinelli
Department of Experimental Medicine and Pathology
University La Sapienza
Rome, Italy
List of contributors xvii

David S. Rampton
Department of Adult and Paediatric Gastroenterology
St. Bartholomew’s and The Royal London School of Medicine and Dentistry
London E1 2AD, UK

Margaret L. Rand
Division of Hematology/Oncology
The Hospital for Sick Children
Toronto
Ontario, Canada

A. Koneti Rao
Division of Hematology and Thromboembolic Diseases
Temple University Health Sciences Center
Room 300 OMS
3400 N. Broad Street
Philadelphia
PA 19140, USA

Giuseppe Remuzzi
Mario Negri Institute for Pharmacological Research
Via Gavazzeni 11
24125 Bergamo, Italy

Francine Rendu
Centre de médecine préventive cardiovasculaire
Hôpital Broussais
96 rue Didot
75014 Paris, France

Juan A. Rosado
Department of Physiology
University of Cambridge
Downing Street
Cambridge CB2 3EG, UK

Harris Rose
Wafic Said Molecular Cardiology and Gene Therapy Research Laboratory and Cullen Research Laboratory
Texas Heart Institute
University of Texas Medical School
Houston
Texas, USA

Zaverio M. Ruggeri
Division of Experimental Hemostasis and Thrombosis
Department of Molecular and Experimental Medicine
The Scripps Research Institute
10555 North Torrey Pines Road
La Jolla
CA 92037, USA

Stewart O. Sage
Department of Physiology
University of Cambridge
Downing Street
Cambridge CB2 3EG, UK

Maria G. Scudillo
Department of Medicine and Aging
Division of Pharmacology
‘G. D’Annunzio’ University of Chieti
Via dei Vestini, 31
66013 Chieti, Italy

Sanford J. Shattil
Department of Vascular Biology
The Scripps Research Institute
10550 North Torrey Pines Road, VB-5
La Jolla
CA 92037, USA

Harnath S. Shelat
Wafic Said Molecular Cardiology and Gene Therapy Research Laboratory and Cullen Research Laboratory
Texas Heart Institute
University of Texas Medical School
Houston
Texas, USA

Masamichi Shiraga
Department of Internal Medicine and Molecular Science
Graduate School of Medicine, B5
Osaka University
2–2 Yamada-oaka, Suita
Osaka 565–0871, Japan

Pia R-M. Siljander
University of Cambridge
Department of Biochemistry
Cardiovascular Biology Section
Building O
Downing Site
Cambridge CB2 1QW, UK

Jan J. Sixma
University Medical Center
Department of Haematology
Room G03.647
P.O. Box 85500
3508 GA Utrecht
The Netherlands
List of contributors

G. Tchernia
Unité d’Immunologie Plaquettaire
INTS
6 rue A. Cabanel
75015 Paris, France

Perumal Thiagarajan
Vascular Biology Research Center and Division of Hematology
University of Texas Medical School
Houston
Texas 77030, USA

Yoshiaki Tomiyama
Department of Internal Medicine and Molecular Science
Graduate School of Medicine, B5
Osaka University
2–2 Yamada-oka, Suita
Osaka 565–0871, Japan

Eric J. Topol
Department of Cardiovascular Medicine
The Cleveland Clinic Foundation – Clinic Centre
9500 Euclid Avenue
Cleveland
Ohio, USA

Mauro Torti
Department of Biochemistry
University of Pavia
via Bassi 21
27100 Pavia, Italy

Chris Van Geet
Department of Paediatrics
University Hospital Leuven, Belgium

Raymond Verhaeghe
Department of Molecular and Cardiovascular Research
University of Leuven Campus
Gasthuisberg O & N
Herestraat 49
Leuven
B-3000, Belgium

Peter Verhamme
Cardiovascular Research Unit of the Center for Experimental Surgery and Anesthesiology
KU Leuven
University of Leuven
Campus Gasthuisberg
O&N Herestraat 49
B-3000 Leuven, Belgium

Jos Vermylen
Centre for Molecular and Vascular Biology
University of Leuven
Herestraat 49
B-3000 Leuven, Belgium

Roberta Vezza
Maxia Pharmaceuticals, Inc.
10835 Altman Row
San Diego, CA 92121, USA

Francesco Violi
University of Rome La Sapienza
Institute of Clinical Medicine 1
00185 Rome, Italy

Jerry Ware
Division of Experimental Hemostasis and Thrombosis
Department of Molecular and Experimental Medicine
The Scripps Research Institute
10555 North Torrey Pines Road
La Jolla
CA 92037, USA

Steve P Watson
Department of Pharmacology
University of Oxford
Mansfield Road
Oxford OX1 3QT, UK

Kathryn E. Webert
Department of Medicine
Faculty of Health Sciences
McMaster University
Hamilton
Ontario, Canada
List of contributors

James G. White
University of Minnesota
Laboratory of Medicine and Pathology
Mayo Box 490
Minneapolis
MN 55455, USA

James T. Willerson
University of Texas Medical School
7000 Fannin, Suite 1700
Houston
TX 77030, USA

Scott Willoughby
Cardiology Unit
The Queen Elizabeth Hospital
28 Woodville Road
Woodville, S. Australia 5011

Kenneth K. Wu
Vascular Biology Research Center and Division of Hematology
University of Texas Medical School
Houston
Texas 77030, USA

Salim Yusuf
Division of Cardiology
Hamilton Health Sciences Corporation
McMaster University
Hamilton, Canada

Pierre Zoldhelyi
Wafic Said Molecular Cardiology and Gene Therapy Research Laboratory and Cullen Research Laboratory
Texas Heart Institute
University of Texas Medical School
Houston
Texas, USA
Blood platelets have attracted an increasing interest among clinicians and basic scientists over the last three decades due to the progressive understanding of the role that these cells play in different physiological phenomena and pathological conditions. Indeed, blood platelets not only participate in normal hemostasis and are a central element in atherothrombosis but are also involved in inflammatory and allergic reactions, in some forms of gastrointestinal, renal and dermatological disorders, in tumour metastasis and in viral, bacterial and parasitic diseases. It is impressive to realize that blood platelets play a primary role, or are involved, in the diseases responsible for the large majority of disability and death worldwide, and namely not only in myocardial infarction, stroke or peripheral vascular disease but also in cancer and its dissemination and several types of infection. Moreover, platelets, due to their easy sampling and to the fact that they possess a rather complex and complete signal transduction machinery typical of excitable cells, are often taken as a model for neurochemical, biochemical and molecular biology studies. It is also important to underline that, based on the expanding knowledge of platelet biology and pharmacology, recent developments in the field of antiplatelet agents have led to relevant therapeutic advancements with great excitement among cardiologists, neurologists, angiologists and internists.

The wide interest that platelets raise among clinicians and basic investigators is reflected in an explosive, exponential increase of publications involving platelets. It seemed thus useful to finally provide a comprehensive, detailed, up-to-date text for clinicians and basic scientists collecting all the available information on platelet structure, function, participation in disease, pharmacology and therapeutics. Provided the book will meet with the interest of the readership, it is planned that new editions updating the advances on this topic will be published every 3–4 years.
The book has been organized in five sections covering platelet physiology, laboratory methodological aspects, platelet involvement in disease, subdividing the latter into hemostatic and non-hemostatic conditions, platelet pharmacology and finally antiplatelet treatment in the clinic. Within these sections, 72 chapters cover all conventional and unconventional aspects of platelet function, involvement in disease or therapeutics. An emphasis was given to novel or upcoming aspects of platelet physiology, pharmacology and therapeutics, such as gene regulation of platelet function, pharmacogenetics, gene therapy, etc. A large group of leading experts and some of the ‘fathers’ of modern platelet studies have willingly accepted to contribute to the book, making up an outstanding crew of 157 scientists coming from disparate fields and thus giving a real interdisciplinary view of the subject. All chapters have been edited for homogeneity and to help in providing a balanced view of the various subjects. It is, of course, impossible to avoid some degree of overlap and repetition in such a book, but it was the intention of the Editors that, especially on some important or hot topics, the subject would be discussed and presented from different angles. An effort to provide schemes and tables with easy-to-read take-home messages has been made; extensive and updated bibliographic citations are given to provide the interested reader with access to greater detail than can be included in an already large book. Many investigators and clinicians, even if not primarily interested in platelets, cross the platelet field in their daily work; this book should serve them as a comprehensive and authoritative guide to the diagnosis and therapeutics of diseases involving platelets.

Our thanks go first of all to the authors who have accepted to spend a considerable amount of their busy time in writing their chapters, undergoing pressure to adhere to a tight time schedule and requests to revise and update their work. The preparation of this book would not have been possible without the help of our editorial assistants and of several coworkers in the Institutions of the individual editors. An excellent collaboration with some members of Cambridge University Press, in particular Richard Barling, Mary Sanders and Lucille Murby, has helped in pushing forward what, in some moments, seemed to be a titanic task in a reasonably rapid, though to us exasperatedly slow, way. Looking back, having forgotten the long tiring hours spent on the project, the preparation of this book has been interesting, enriching and amusing to us; we hope it will also be so for the readers.

The Editors
Paolo Gresele
Clive P. Page
Valentin Fuster
Jos Vermylen