Therapeutic Angiogenesis for Vascular Diseases
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Molecular Mechanisms and Targeted Clinical Approaches for the Treatment of Angiogenic Disease
Angiogenesis is a term used to identify a process of formation of new blood vessels from pre-existing ones. In 1971, Judah Folkman published a paper in the New England Journal of Medicine proposing, for the first time, that tumour growth is angiogenic-dependent. He also proposed that blocking the growth of the vasculature surrounding the tumour could lead to tumor growth arrest or even tumor regression. However, at that time, this idea was criticized by many biologists, because the prevailing opinion was that the host immune system would play a more important role than angiogenesis in tumour progression.

One year later, Michael Gimbrone, a student working in Folkman’s laboratories, demonstrated that tumour specimens implanted into the corpus vitreum of an eye, which is avascular, did not grow. By contrast, if the tumour specimen was implanted close to the retina, which is rich in vessels, it grew rapidly, forming a mass a thousand times bigger than that initially implanted. However, a number of years passed before scientists were convinced that Folkman’s idea was right.

In 1980 I was a Visiting Fellow at the Pathophysiology Department of the National Institute of Health and National Cancer Institute in Bethesda. My tutor was the late Dr. Pietro Maria Gullino. Although less famous than Folkman, he can be considered another “father of angiogenesis”. He did not need to spend a lot of time convincing me that the process of angiogenesis was important in cancer. Since he was a pathologist, he also suggested to me to continue studying the angiogenesis process and, in particular, to focus my attention on endothelial cell biology, because, as he said: “Besides cancer, the abnormal behavior of these cells may give rise to many other different human diseases”.

Today, almost 30 years have passed. The impressive number of papers published on angiogenesis (several thousands of papers, with a peak of 3000 in 2003) is the best proof of the importance of angiogenesis in human diseases. Thanks to the ground-breaking discoveries of Napoleone Ferrara and Harold Dvorak, who both discovered the vascular endothelial growth factor (VEGF), a protein that plays a fundamental role in neovessel formation, and thanks to the late Jeffery Isner, who was a pioneer in applying VEGF to patients in a clinical setting, angiogenesis nowadays still represents one of the major fields of research world wide.

Scientists are investigating the role of angiogenesis in a broad spectrum of human diseases. They are looking for factors that may inhibit the angiogenic process in
order to fight cancer, diabetic retinopathy, inflammation, atherosclerosis etc., or vice versa they are searching for molecules that may enhance the angiogenic process in order to treat patients with ischemic diseases such as stroke, heart infarct and limb ischemia. Many of these diseases cannot be treated with conventional therapy.

Recently, the field of angiogenic research has accelerated because some molecules have reached the bedside. Now around twenty anti-angiogenic drugs are being tested as anti-cancer agents in human clinical trials, (some of them have reached phase III, the last phase of investigation). It is still too soon to say which could be effective in fighting cancer. However, one of them, Avastin is actually in clinical use for the treatment of colon cancer. There are also clinical trials investigating molecules that improve angiogenesis.

Besides the use of drugs, a very new strategy to treat patients with ischemic disease combines the use of stem cells and gene therapy. This strategy of using stem cells by itself, or cells ex vivo engineered to transport angiogenic molecules, represents the most advanced frontier in angiogenesis research opening new avenues for regenerative medicine.

Mark Slevin is a leading scientist in angiogenesis research. He is particularly involved in studying the molecular mechanism in vessel formation focused on cancer, stroke, atherosclerosis and diabetes. Since 1993 I have appreciated his work; he was investigating the molecular mechanism of gangliosides in the control of endothelial cell proliferation. Today he is investigating the involvement of TGF beta and its co-receptor CD105 in tumour and diabetic retinopathy related angiogenesis. He has now edited a book focused on therapeutic angiogenesis and its potential application on human pathologies.

This book covers almost all of the major diseases in which excessive or reduced angiogenesis may concur to human pathologies. Compared with other edited books on angiogenesis, this book has an additional value, because it also offers new insight into the role of angiogenesis in neurodegenerative diseases and, in particular, a section on Alzheimer’s disease and neurodegeneration associated with dementia. Indeed, there is new evidence that neovascularization may also be linked to the development of these diseases.

Finally this book gathers up a significant number of top scientists. Every one of the authors is an expert in a particular branch of angiogenesis research discussed within the book. I sincerely hope that this book will receive the appropriate interest in reading, not only by experts of angiogenesis, but also by younger investigators who will be helped by this text in completing their scientific background in the fields of angiogenesis research.

Fondazione IRCCS Neurological Institute “Carlo Besta”       Giulio Alessandri
Milan Italy                                                 December 2009
Preface

Over the last 20 years, the importance of the process of angiogenesis (the growth of new blood vessels) both in health and disease has been investigated in more and more detail. The numbers of publications cited in public databases in this field of research increases significantly year by year as new findings demonstrate novel mechanisms through which this process can modulate disease development and recovery.

This volume is dedicated solely to a description of our current understanding of these mechanisms and how manipulation of angiogenesis can be used therapeutically to benefit treatment.

Pathological angiogenesis is intimately associated with almost all of the major diseases afflicting human life and excessive angiogenesis results in, for example, more rapid solid tumour development and metastasis (cancer); atherosclerosis and subsequent development of unstable plaques resulting in myocardial infarction (MI) or stroke; and proliferative retinopathy in diabetic patients. Conversely, increased angiogenesis can benefit patients in terms of wound recovery, improvement in tissue reperfusion after stroke and MI, and in peripheral vascular disease, and may be an important feature conferring protection against the onset of neurodegenerative diseases such as Alzheimer’s.

For these reasons, understanding the factors/cellular mechanisms responsible for modulating the ‘angiogenic switch’ should be the key to defining improved clinical regimens for maximisation of patient benefit. Developments in this field have extended beyond clinical trials and in some cases angiogenic therapy is now a regular part of patient therapy. Chapter by chapter, this volume sets out to describe the current treatment options, experimental therapies and future perspectives, starting with an overview of the normal processes of wound healing and the influence and importance of angiogenesis. Dr Heike Hall-Bozic will describe this process as well as a novel 3-dimensional scaffold system for controlled release of angiogenic molecules and stimulation of tissue recovery.

Subsequent chapters written by renowned experts in their chosen field will then describe the process and mechanism of vascularization and current state-of-the-art technology applied to angiogenesis for maximisation of treatment.

Other chapters describe important angiogenesis-diseases with a focus on targeted approaches to treatment. Anti-angiogenic therapy is a promising tool for the
treatment of vasoproliferative retinopathies and Dr Jian-Xing Ma will describe the processes responsible for development of these diseases and current methods of clinical control. Drs Jones, McFarland and Stout will go on to describe the potential of gene therapy applied to inhibit angiogenesis. Two separate chapters will investigate the importance of angiogenesis in tumour development and metastasis. Dr Jan Kitajewski and co-authors will describe the involvement of angiogenesis in these processes whilst Dr Yihai Cao will focus on anti-angiogenic cancer therapy.

Angiogenesis is an important process responsible for determining tissue reperfusion after stroke, a key factor associated with neuronal survival and patient recovery. We have therefore devoted several chapters of the book to a description of cellular signalling mechanisms of re-vascularization (Dr Heike Beck), the relationship between angiogenesis and neural re-integration (Drs Erin Lavik and Joseph Madri), and finally an insight into possible therapeutic angiogenic strategies (Drs Panya Manoonkitiwongsa, Robert Schultz and Patrick Lyden).

Similarly, excessive growth of new blood vessels plays an important role in the developmental phase of atherosclerosis and perhaps more importantly in the later stages of unstable plaque development and is an important factor contributing to thrombosis. In this book, we have discussed the evidence for association of angiogenesis with unstable plaque formation and rupture (Drs Frank Kolodgie, Aloeke Finn, Jagat Narula and Renu Virmani), focussed specifically on the role of haptoglobin, macrophages and the heme-oxygenase system (Drs K-Raman Purushothaman, Meerarani Purushotaman, Andrew Levy, Samin Sharma, Valentin Fuster and Pedro Moreno), and finally, examined therapeutic approaches for inhibition of plaque angiogenesis (Drs Konstantinos Toutouzas, Andreas Synetos and Christodoulos Stefanidis). Plaque build up in peripheral arteries also results in reduced blood flow, usually in the legs and concurrent oxygen starvation of the muscles resulting in impairment of mobility. Drs Philip Bennett, Stanley Silverman, Paramjit Gill and Greg Lip will discuss the possibility of using therapeutic vessel regeneration to treat peripheral vascular disease.

Stimulation of angiogenesis in damaged, hypoxic cardiac tissue has been shown to result in formation of collateral blood vessels, thus increasing the blood supply and improving tissue repair. Drs John O’Sullivan, Anne-Laure Leblond and Noel Caplice will discuss this in Chapter 14.

Over the last few years, mounting evidence has shown a link between development of Alzheimer’s disease and brain neovascularization or microvessel collapse in susceptible regions containing β-amyloid plaques. In this book, we will describe evidence for the association of angiogenic mediators with Alzheimer’s pathology (Dr Paula Grammas), and consider the association between ischaemic stroke (particularly lacunar), vascular development and neurodegenerative disease with a view to identification of novel clinical intervention (Drs Adria Arboix, Marta Grau-Olivares and Jerzy Krupinski).

The book will finish with a series of chapters dedicated to specific diseases in which angiogenesis is known to have an important association with pathophysiological development, and with a focus to possible future therapeutic manipulation. Drs Serafim Kiriakidis and Ewa Paleolog will discuss the importance of angiogenesis in
pathogenesis of arthritis, and novel treatments, Drs Sarah Mackie, Ann Morgan and Pamela Jones will talk about microvessel formation in giant cell arthritis, and Drs Ahmed Itrat and Ayeesha Kamal will examine collateral blood vessel development in MoyaMoya disease and possible treatment regimens.

The final chapter, written by Judith Sendra-Cuadal, Merce Morral and Marc Ramis-Castelltort offers an insight into how nanotechnology may be utilised to improve the efficiency of current angiogenesis therapies in key disease processes and serves as an appropriate way to finish off this volume.

London, UK  
Mark Slevin
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Contributors

Giulio Alessandri  Neurobiology and Neuroregenerative Therapies Unit, Fondazione IRCCS Neurological Institute “Carlo Besta”, Milan, Italy, cisiamo2@yahoo.com

Adria Arboix  Cerebrovascular Division, Department of Neurology, Hospital Universitari del Sagrat Cor, Universitat de Barcelona, C/Viladomat288, E-08029, Barcelona, Spain, aarboix@hscor.com

Heike Beck  Walter Brendel Center of Experimental Medicine, Institute of Cardiovascular Physiology, Ludwig-Maximilians University Munich, Marchioninistr. 27, 81377 Munich, Germany, Heike.Beck@med.uni-muenchen.de

Philip C. Bennett  Research Fellow, University Department of Medicine, City Hospital, Birmingham B18 7QH, UK; Department of Vascular Surgery, City Hospital, Birmingham B18 7QH, UK, philip.bennett@doctors.org.uk

Yihai Cao  Department of Microbiology, Tumor and Cell Biology, Karolinska Institute, 171 77 Stockholm, Sweden, g.y.h.lip@bham.ac.uk

Noel M. Caplice  Centre for Research in Vascular Biology, Biosciences Institute, University College Cork, Cork, Ireland, n.caplice@ucc.ie

Judith Sendra Cuadal  Endor Nanotechnologies, Baldiri Reixac 15, 08028 Barcelona, Spain, judith.sendra@endornanotech.com

Aloke V. Finn  Department of Internal Medicine, Emory University School of Medicine, Atlanta, GA, USA, avfinn@emory.edu

Valentin Fuster  From the Zena and Michael A. Wiener Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY, USA, valentin.fuster@mssm.edu

Paramjit Gill  Reader in Primary Care Research, Department of Primary Care and General Practice University of Birmingham, Edgbaston, Birmingham B15 2TT, England, p.s.gill@bham.ac.uk
Paula Grammas  Garrison Institute on Aging, and Department of Neurology, Texas Tech University Health Sciences Center, Lubbock, TX, USA, paula.grammas@ttuhsc.edu

Marta Grau-Olivares  Cerebrovascular Division, Department of Neurology, Hospital Universitari del Sagrat Cor, Universitat de Barcelona, C/Viladomat288, E-08029, Barcelona, Spain, martagrau76@hotmail.com

Heike Hall  Department of Materials, HCI E415, Cells and BioMaterials, Wolfgang-Pauli-Strasse 10, CH-8093 Zurich, Switzerland, heike.hall@mat.ethz.ch

Ahmed Itrat  Stroke Service, Section of Neurology, Department of Medicine, Aga Khan University Hospital, Karachi, Pakistan, ahmeditrat@gmail.com

Jacob M. Jones  Casey Eye Institute, Oregon Health and Science University, Portland, OR, USA, jjones@ohsu.edu

Pamela F. Jones  Leeds Institute of Molecular Medicine, University of Leeds, Leeds, UK, p.jones@leeds.ac.uk

Ayeesha Kamal  Stroke Service, Section of Neurology, Department of Medicine, Aga Khan University Hospital, Karachi, Pakistan, ayeesha.kamal@aku.edu

Jessica J. Kandel  Surgery, Herbert Irving Comprehensive Cancer Center, 1130 St. Nicholas Avenue, New York, 10032 NY, USA, jjk47@columbia.edu

Serafim Kiriakidis  Kennedy Institute of Rheumatology, Faculty of Medicine, Imperial College, Arthritis Research Campaign Building, 65 Aspenlea Road, London W6 8LH, UK, s.kiriakidis@imperial.ac.uk

Jan Kitajewski  Pathology, Obstetrics and Gynecology, Columbia University Medical Center, 1130 St. Nicholas Avenue, New York, 10032, NY, USA, jkk9@columbia.edu

Frank D. Kolodgie  From the CVPath Institute, Inc., Gaithersburg, MD, USA, fkolodgie@vpath.org

Jerzy Krupinski  Hospital Universitari Mútua de Terrassa, Department of Neurology, Cerebrovascular Diseases Unit, Pl. Dr. Robert, 5, 08221 Terrassa, Barcelona, Spain, jkrupinski@mutuaterrassa.es

Erin Lavik  Department of Biomedical Engineering, Case Western Reserve University, Wickenden Building, 10900 Euclid Avenue, Cleveland, 44106-7207 OH, USA, erin.lavik@case.edu

Anne-Laure Leblond  Centre for Research in Vascular Biology, Biosciences Institute, University College Cork, Cork, Ireland, al.leblond@ucc.ie

Andrew P. Levy  From the Zena and Michael A. Wiener Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY, USA, alevy@tx.technion.ac.il
Contributors

**Gregory Y.H. Lip**  Professor of Cardiovascular Medicine, University Department of Medicine, City Hospital, Birmingham, B18 7QH, UK, g.y.h.lip@bham.ac.uk

**Patrick D. Lyden**  Professor of Neurosciences & Medical Director of Stroke Center, Department of Neurosciences & UCSD Stroke Center, University of California – San Diego, La Jolla, CA, USA, plyden@ucsd.edu

**Jian-xing Ma**  Department of Cell Biology, Department of Medicine, The University of Oklahoma Health Sciences Center, 941 Stanton L. Young Blvd, Oklahoma City, OK, USA, jian-xing-ma@ouhsc.edu

**Sarah L. Mackie**  Leeds Musculoskeletal Biomedical Research Unit, Leeds Institute of Molecular Medicine, University of Leeds, Leeds, UK, s.l.mackie@leeds.ac.uk

**Joseph A. Madri**  Department of Pathology, Yale University School of Medicine, 310 Cedar Street, P.O. Box 208023, New Haven, 06520-8023 CT, USA, joseph.madri@yale.edu

**Panya S. Manoonkitiwongsa**  Chief of Histology, Neuroanatomy & Experimental Neuropathology, Neural Engineering Program, Huntington Medical Research Institutes, Pasadena, CA, USA, stevemanoon@hotmail.com

**Trevor McFarland**  Casey Eye Institute, Oregon Health and Science University, Portland, OR, USA, mcfarlandt@ohsu.edu

**Pedro R. Moreno**  From the Zena and Michael A. Wiener Cardiovascular Institute, Mount Sinai School of Medicine, New York, USA, pedro.moreno@msnyuhealth.org

**Ann W. Morgan**  Leeds Musculoskeletal Biomedical Research Unit, Leeds Institute of Molecular Medicine, University of Leeds, Leeds, UK, a.w.morgan@leeds.ac.uk

**Mercè Morral**  Department of Ophthalmology, Hospital Clínic i Provincial de Barcelona, University of Barcelona, Spain, merce.morral@gmail.com

**Jagat Narula**  University of California, Irvine School of Medicine, Irvine, CA, USA, narula@uci.edu

**John F. O’Sullivan**  Centre for Research in Vascular Biology, Biosciences Institute, University College Cork, Cork, Ireland, osull.john@gmail.com

**Ewa M. Paleolog**  Kennedy Institute of Rheumatology, and Division of Surgery, Oncology, Reproductive Biology and Anaesthetics, Faculty of Medicine, Imperial College, Arthritis Research Campaign Building, 65 Aspenlea Road, London W6 8LH, UK, e.paleolog@imperial.ac.uk
Contributors

**K-Raman Purushothaman** From the Zena and Michael A. Wiener Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY, USA, purushothaman.kothandaram@mountsinai.org

**Meerarani Purushothaman** From the Zena and Michael A. Wiener Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY, USA, meerarani.purushothaman@msnyuhealth.org

**Marc Ramis-Castelltort** Endor Nanotechnologies, Baldiri Reixac 15, 08028, Barcelona, Spain, marc.ramis@endornanotech.com

**Robert L. Schultz** Professor of Anatomy, Department of Pathology & Human Anatomy, Loma Linda University, Loma Linda, CA, USA

**Samin K. Sharma** From the Zena and Michael A. Wiener Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY, USA, samin.sharma@mountsinai.org

**Stanley Silverman** Consultant Vascular Surgeon, Department of Vascular Surgery, City Hospital, Birmingham, B18 7QH, UK, s.h.silverman@bham.ac.uk

**Christodoulos Stefanadis** First Department of Cardiology, Hippokration Hospital, Athens Medical School, Athens, Greece, constantin.stefanidis@ulb.ac.be

**J. Timothy Stout** Casey Eye Institute, Oregon Health and Science University, 3375 SW Terwilliger Ave, Portland, 97239 OR, USA, stoutt@ohsu.edu

**Andreas Synetos** First Department of Cardiology, Hippokration Hospital, Athens Medical School, Athens, Greece, synetos@yahoo.com

**Konstantinos Toutouzas** First Department of Cardiology, Hippokration Hospital, Athens Medical School, Athens, Greece, ktoutouz@otenet.gr

**Renu Virmani** From the CVPath Institute, Inc., Gaithersburg, MD, USA, virmani@afip.osd.mil

**Darrell J. Yamashiro** Pediatrics, Pathology, Herbert Irving Comprehensive Cancer Center, Columbia University Medical Center, 1130 St. Nicholas Avenue, New York, 10032 NY, USA, dy39@columbia.edu

**Bin Zhang** Department of Cell Biology, Department of Medicine, The University of Oklahoma Health Sciences Center, 941 Stanton L. Young Blvd, Oklahoma City, OK, USA, bin-zhang@ouhsc.edu