Gustav Steinhoff *Editor*

Regenerative Medicine

from Protocol to Patient

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Editor
Gustav Steinhoff, M.D., Ph.D.
Professor of Cardiac Surgery, Director
Medical Faculty, Department of Cardiac Surgery
and
Reference and Translation Center of Cardiac Stem Cell Therapy (RTC)
University of Rostock, Schillingallee 35, 18057 Rostock, Germany
gustav.steinhoff@med.uni-rostock.de

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Foreword

Regenerative Medicine is a fastly emerging interdisciplinary field of research and clinical therapies on the repair, replacement or regeneration of cells, tissues or organs in congenital or acquired disease. This new field of research and clinical development focussing on stem cell science and regenerative biology is just starting to be the most fascinating and controversial medical development at the dawn of the twenty-first century. It can be envisaged that this development will establish completely new molecular and cellular techniques for medical therapy. An early scientific trigger was set more than 100 years ago by the physiology of blood regeneration (Hall and Eubanks 1896) and successful vascular surgical techniques for organ transplantation (Carrel and Guthrie 1905). However, the clinical realization of allogenic blood transfusion lasted until the discovery of the blood group antigens (Landsteiner and Levine 1928) and successful routine allogenic organ and bone marrow transplantation even until the end of the last century.

Similar to the field of allogenic cell and organ transplantation it seems that *Regenerative Medicine* again condenses mankind's visions, hopes, and fears regarding medicine: Hopes of eternal life and effective treatment of uncurable disease as well as fears of misuse of technology and uncontrolled modifications of life are polarizing the scientific field. The development and public acceptance of new ethical and regulatory guidelines is a necessary process to support the further clinical development. Nevertheless, the vision of a new medicine using the regenerative power of biology to treat disease and restructure the organism is setting the aim for scientific, technological and medical development. Viewing the great expectations to restructure and regenerate tissue, organs or organisms the current attempts of scientist and physicians are still in an early phase of development.

The field of *Regenerative Medicine* has developed rapidly over the last 20 years with the advent of molecular and cellular techniques. This new textbook on *Regenerative Medicine: From Protocol to Patient* is aiming to explain the scientific knowledge and emerging technology as well as the clinical application in different organ systems and diseases. The international leading experts from four continents describe the latest scientific and clinical knowledge of the field of "Regenerative Medicine". The process of translating science of *laboratory protocols into therapies* is explained in sections on regulatory, ethical and industrial issues. Patient needs are advocated by the proposition initiatives on the scientific development of new therapies.

This textbook is organized into five major parts: *(I) Biology of Tissue Regeneration, (II) Stem Cell Science and Technology, (III) Tissue Engineering, Biomaterials and Nanotechnology, (IV) Regenerative Therapies, and (V) Regulation and Ethics.*

We start with an overview on the *History of Regenerative Medicine*. This is followed by the part of *Biology of Tissue Regeneration*, which focuses on extracellular matrix, asymmetric stem cell division, stem cell niche regulation and stem cells during embryonic neurogenic development. The part on *Stem Cell Science and Technology* provides an overview as classification of stem cells and describes techniques for their derivation and culture. Basic properties of the cells are illustrated, and some areas of applications for these cells are discussed with emphasis on their possible future use in *Regenerative Medicine*.

The part of *Tissue Engineering, Biomaterials and Nanotechnology* focuses on the development of technologies, which enable an efficient transfer of therapeutic genes and drugs exclusively to target cells and potential bioactive materials for clinical use. Chimerism, multifunctionalized nanoparticles and nanostructured biomaterials are described with regard to the technological development of new clinical cell technology.

The part on *Regenerative Therapies* gives a survey on the clinical development in the different organ systems. Disease specific approaches of new therapies, application technology, clinical achievements and limitations are described. The part on *Regulation and Ethics* describes the current legislation for clinical translation as the ethical and juridical development in different countries. The need for patient propositions to foster the scientific development and clinical translation is described by Robert Klein, initiator of the California Initiative of Regenerative Medicine (CIRM).

The textbook is aiming to give the student, the researcher, the health care professional, the physician, and the patient a complete survey on the current scientific basis, therapeutical protocols, clinical translation and practised therapies in *Regenerative Medicine*. On behalf on the sincere commitment of the international experts we hope to increase your knowledge understanding, interest and support by reading the book.

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Gustav Steinhoff, M.D., Ph.D. (Editor)
Hoang Tu-Rapp, Ph.D. (Assistant Editor)

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Prof. Dr. med. Gustav Steinhoff
Professor of Cardiac Surgery
Director
Department of Cardiac Surgery
and
Reference and Translation Center of Cardiac Stem Cell Therapy (RTC)
Medical Faculty
University of Rostock
Schillingallee 35
18057 Rostock
Germany

Dr. Hoang Tu-Rapp
Department of Cardiac Surgery
Medical Faculty
University of Rostock
Schillingallee 35
18057 Rostock
Germany

Contents

Contributors

Yoko Arai
Max-Planck-Institute of Molecular Cell Biology and Genetics,
Pfotenhauerstr. 108, D-01307 Dresden, Germany

Takayuki Asahara, M.D., Ph.D
Group of Vascular Regeneration Research,
Institute for Biomedical Research and Innovation (IBRI)/RIKEN
Center for Developmental Biology, 2-2-3 Minatojima-Minamimachi,
650-0047 Chuo-ku, Kobe-shi Hyogo, Japan

Augustinus Bader, M.D
Medical Faculty, Biotechnological-Biomedical Center (BBZ),
Leipzig University, Deutscher Platz 5, 04103 Leipzig, Saxony, Germany

Silvia Baiguera, Ph.D
BIOAIR LAB, Department of General Thoracic and Regenerative Surgery,
and Intrathoracic Biotransplantation, University Hospital Careggi,
Largo Brambilla 3, 50141 Florence, Italy

Dorairajan Balasubramanian, Ph.D
Prof Brien Holden Eye Research Centre, L.V. Prasad Eye Institute,
Banjara Hills, 500 034 Hyderabad, AP, India

Murali MS Balla
Champalimaud Translational Centre for Eye Research,
Hyderabad Eye Research Foundation,
L.V. Prasad Eye Institute, L.V. Prasad Marg,
Banjara Hills, Hyderabad, India 500 034

Sharmila A. Bapat, Ph.D
National Centre for Cell Science, NCCS Complex, Pune University Campus,
Ganeshkhind, Pune, Maharashtra, India 411 007

Gregor Becker, Ph.D
Group for Bio-Ethics in Life Sciences (GBLS), Faculty of Biochemistry,
Biophysics and Biotechnology, Jagiellonian University, ul. Gronostajowa 7,
Kraków 30-387, Poland

A. Berner, M.D
Queensland University of Technology,
60 Musk Avenue, Kelvin Grove, QLD 4059, Australia

Ute Bissels
Miltenyi Biotec GmbH, Friedrich-Ebert-Straße 68,
51429 Bergisch Gladbach, Germany

Michael Bock, Ph.D
TWINCORE, Centre for Experimental and Clinical Infection Research,
Joint venture between Helmholtz Centre for Infection Research (HZI) in
Braunschweig and the Hannover Medical School (MHH), Feodor-Lynen-Str. 7-9,
30625 Hannover, Germany

Andreas Bosio
Miltenyi Biotec GmbH, Friedrich-Ebert-Straße 68,
51429 Bergisch Gladbach, Germany

Christoph Brenner, M.D
Department of Internal Medicine, University of Munich – Campus Grosshadern,
Marchioninistrasse 15, Munich D-81377, Germany

Federico Calegari, Ph.D
Group Leader, Center for Regenerative Therapies,
Technische Universität Dresden,
c/o: Max-Planck-Institute of Molecular Cell Biology and Genetics,
Pfotenhauerstr. 108, D-01307 Dresden, Germany

Tobias Cantz
Junior Research Group "Stem Cell Biology",
Cluster of Excellence REBIRTH, Hannover Medical School,
Carl-Neuberg-Str. 1, 30623 Hannover, Germany

Maurizio C. Capogrossi, M.D
Director, Professor, Laboratorio di Patologia Vascolare,
Istituto Dermopatico dell' Immacolata (IDI)-Istituto di
Ricovero e Cura a CarattereScientifico (IRCCS),
Via Monti di Creta 104, I-00167 Rome, Italy

Lavinia Coltan, M.D
Department of Physiology, Women and Children's Health Research Institute,
University of Alberta, Edmonton, AB, Canada

Sabine Conrad
Institute of Anatomy, Department of Experimental Embryology
and Center for Regenerative Biology and Medicine,
University of Tübingen, Österbergstr. 3, Tübingen 72074, Germany

Robert David, Ph.D
Department of Internal Medicine, University of Munich – Campus Grosshadern,
Marchioninistrasse 15, Munich D-81377, Germany

Georg N. Duda, Ph.D
Julius Wolff Institute and Centre for Musculoskeletal Surgery,
Berlin-Brandenburg Centre for Regenerative Therapy, Charité,
Augustenburgerplatz 1, Berlin 13353, Germany

Mikael C.O. Englund, Ph.D
Site Manager and Senior Scientist,
Cellartis AB, 1 Würzburg Court, Dundee,
DD2 1FB, UK

Joshua O. Eniwumide, Ph.D
Julius Wolff Institute and Centre for Musculoskeletal Surgery,
Berlin-Brandenburg Centre for Regenerative Therapy, Charité,
Augustenburgerplatz 1, Berlin 13353, Germany

Jonathan Frampton, B.A., Ph.D
Institute of Biomedical Research College of Medicine &
Dental Science, University of Birmingham, Edgbaston,
Birmingham B15 2TT, UK

Wolfgang-Michael Franz, M.D
Department of Internal Medicine, University of Munich – Campus Grosshadern,
Marchioninistrasse 15, Munich D-81377, Germany

Mathias Freund, M.D., Ph.D
Professor and Chairman, Department of Internal Medicine III,
University of Rostock, Ernst-Heydemann-Strasse 6,
Rostock 18057, Germany

Kristina Arvidson Fyrberg, D.D.S., Ph.D
Department of Clinical Dentistry – Centre for Clinical Dental Research,
University of Bergen, Årstadveien 17, 5020 Bergen, Norway

Elisa Gambini
Laboratorio di Biologia Vascolare e Medicina Rigenerativa,
Centro Cardiologico Monzino-IRCCS,
Via Parea 4, 20138 Milan, Italy

Changyou Gao, Ph.D
Department of Polymer Science and Engineering,
Zhejiang University, No. 38, Zheda Road
Hangzhou 310027, China

Anna Grabinski
Faculty of Law and Political Science, Rennes 1 University,
9 rue Jean Macé - CS 54203, Rennes 35042, France

Christina Irene Günter, M.D
Clinic for Plastic and Hand Surgery, University Hospital Rechts der Isar,
Technische Universitaet Muenchen, Ismaninger Str. 22, 81675 Munich,
Bavaria, Germany

Hermann Haller, M.D
Department of Nephrology and Hypertension, Hannover Medical School, Carl-Neuberg-Str. 1, Hannover, Germany

Sølve Hellem, D.D.S., Ph.D
Department of Clinical Dentistry Oral and Maxillofacial Surgery, University of Bergen, Årstadveien 17, 5020 Bergen, Norway

Frank Hirth, B.Sc., M.Sc., Ph.D., P.D
Department of Neuroscience, MRC Centre for Neurodegeneration Research, Institute of Psychiatry, King's College London, 16 De Crespigny Park, Denmark Hill, London SE5 8AF, UK

Anthony D. Ho, M.D., FRCPC
Director/Professor, Department of Medicine V, Heidelberg University, Im Neuenheimer Feld 410, 69120 Heidelberg, Germany

Raymund E. Horch, M.D
Professor/Director, Chairman,
Department of Plastic and Hand Surgery,
University of Erlangen,
Krankenhausstr. 12, 91054 Erlangen, Germany

Dietmar W. Hutmacher, Ph.D., MBA, M.Sc
Institute of Health and Biomedical Innovation, Queensland University of Technology, 60 Musk Avenue, Kelvin Grove QLD 4059, Australia

Wieland B. Huttner, M.D
Director/Professor, Max-Planck-Institute of Molecular Cell Biology and Genetics, Pfotenhauerstr. 108, D-01307 Dresden, Germany

Johan Hyllner, Ph.D
Cellartis AB, Arvid Wallgrens Backe 20, SE-413 46 Göteborg, Sweden

Razvan Iacob
University of Medicine and Pharmacy "Carol Davila", Bucharest, Romania; and, Department of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School; TWINCORE, Centre for Experimental and Clinical Infection Research, Joint venture between Helmholtz Centre for Infection Research (HZI) in Braunschweig and the Hannover Medical School (MHH), Feodor-Lynen-Str. 7-9, 30625 Hannover, Germany

Masaaki Ii, M.D., Ph.D
Department of Pharmacology, Osaka Medical College, Osaka, Japan

Tohru Itoh, Ph.D
Institute of Molecular and Cellular Biosciences,
University of Tokyo, 1-1-1 Yayoi, Bunkyo-ku, Tokyo, Japan

Kewal K. Jain, M.D., FRACS, FFPM
Jain PharmaBiotech, Blaesiring 7, 4057 Basel, Switzerland

Nopporn Jongkamonwiwat, Ph.D
Centre for Stem Cell Biology and Department of Biomedical Sciences,
University of Sheffield, Addison Bldg, Western Bank S10 2TN, Sheffield ,UK

Emilia Kaivosoja, M.Sc. (Engineering)
Department of Medicine, Institute of Clinical Medicine, Haartmaninkatu 8,
00029 HUS, Finland

Atsuhiko Kawamoto, M.D., Ph.D
Regenerative Medicine unit, Institute of Biomedical Research and
Innovation/RIKEN Center for Developmental Biology, Kobe, Japan

Seung U. Kim, M.D., Ph.D
Professor Emeritus of Neurology, Division of Neurology,
Department of Medicine, UBC Hospital, University of British Columbia,
Vancouver, BC V6T 2B5, Canada;

Robert N. Klein II, J.D
Chairman, Governing Board,
California Institute for Regenerative Medicine (CIRM),
210 King Street, Third Floor, San Francisco, CA 94107, USA

Yrjö T. Konttinen, M.D., Ph.D
Professor of Medicine, Department of Medicine, Institute of
Clinical Medicine, Haartmaninkatu 8, 00029 HUS, Finland

Anjali P. Kusumbe
National Centre for Cell Science, NCCS Complex, Pune University Campus,
Ganeshkhind, Pune, Maharashtra, India 411 007

Andreas Lendlein, Ph.D
Center for Biomaterial Development, Institute for Polymer Research
Helmholtz-Zentrum Geesthacht, Kantstrasse, 55, Teltow 14513, Germany

Jaakko Levón, B.Sc. (Med)
Department of Medicine, Institute of Clinical Medicine,
Haartmaninkatu 8, 00029 HUS, Finland

Wenzhong Li, Dr.-ing (NUS)
Group Leader, Medical Faculty, Department of Cardiac Surgery,
University of Rostock, Rostock, Germany

Paolo Macchiarini, M.D., Ph.D
Department of General Thoracic and Regenerative Surgery and Intrathoracic
Biotransplantation, University Hospital Careggi,
Largo Brambilla 3, 50141 Florence, Italy

Hans-Günther Machens, M.D
Professor, Director Clinic for Plastic and Hand Surgery,
University Hospital Rechts der Isar, Technische Universitaet Muenchen,
Ismaninger Str. 22, 81675 Munich, Bavaria, Germany

Zygmunt Mackiewicz, Ph.D., D.Sc
Professor of Medicine, Department of Histology and Embryology,
Medical University of Bialystok, G. Washington Street 13, 15-269
Bialystok, Poland

Michael P. Manns, M.D
Director/Professor, Department of Gastroenterology,
Hepatology and Endocrinology, Hannover Medical School,
30623 Hannover, Germany

Indumathi Mariappan, Ph.D
Prof Brien Holden Eye Research Centre, L.V. Prasad Eye Institute,
Banjara Hills, 500 034 Hyderabad, AP, India

Almudena Martinez-Fernandez, PharmD, Ph.D
Research Fellow, Marriott Heart Disease Research Program,
Division of Cardiovascular Diseases, Departments of Medicine, Molecular
Pharmacology and Experimental Therapeutics and Medical Genetics, Mayo
Clinic, 200 First Street SW, Rochester, MN 55905, USA

Stefan Miltenyi
Miltenyi Biotec GmbH, Friedrich-Ebert-Straße 68, 51429
Bergisch Gladbach, Germany

Thomas Mittlmeier, M.D
Director/Professor, Department of Trauma and Reconstructive Surgery,
University of Rostock, Schillingallee 35, Rostock 18057, Germany

Atsushi Miyajima, Ph.D
Professor, Institute of Molecular and Cellular Biosciences,
University of Tokyo, 1-1-1 Yayoi, Bunkyo-ku, Tokyo, Japan

Kamal Mustafa, D.D.S., Ph.D
Department of Clinical Dentistry – Centre for Clinical Dental Research,
University of Bergen, Årstadveien 17, 5020 Bergen, Norway

Timothy J. Nelson, M.D., Ph.D
Assistant Professor of Medicine, Marriott Heart Disease Research Program,
Division of Cardiovascular Diseases, Departments of Medicine,
Molecular Pharmacology and Experimental Therapeutics, and Medical Genetics,
Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA

Fumitaka Osakada, Ph.D
Systems Neurobiology Laboratory,
The Salk Institute for Biological Studies,
10010 North Torrey Pines Road, La Jolla, CA 92037, USA

Michael Ott, M.D
Professor, Department of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, TWINCORE, Centre for Experimental and Clinical Infection Research, Joint venture between Helmholtz Centre for Infection Research (HZI) in Braunschweig and the Hannover Medical School (MHH), Feodor-Lynen-Str. 7-9, 30625 Hannover, Germany

Maurizio Pesce, Ph.D
Laboratorio di Biologia Vascolare e Medicina Rigenerativa, Centro Cardiologico Monzino-IRCCS, Via Parea, 4, 20138 Milan, Italy

Elias Polykandriotis, M.D
Department of Plastic and Hand Surgery, University of Erlangen, Krankenhausstr. 12, 91054 Erlangen, Germany

Giulio Pompilio, M.D., Ph.D
Dipartimento di Chirurgia Cardiovascolare Laboratorio di Biologia, Vascolare e Medicina Rigenerativa, Centro Cardiologico Monzino-IRCCS Università degli Studi di Milano, Via Parea, 4, 20138 Milan, Italy

Laurentiu M. Popescu, M.D., Ph.D
General Director, Professor, "Victor Babes", National Institute of Pathology, 99-101 Splaiul Independentei, 050096 Bucharest, Romania
Department of Cellular and Molecular Medicine, "Carol Davila" University of Medicine and Pharmacy, Bucharest 35, Romania

Brigitte M. Pützer, M.D., Ph.D
Professor of Molecular Biology, Director,
Department of Vectorology and Experimental Gene Therapy,
Biomedical Research Center, University of Rostock, Schillingallee 69,
Rostoc 18057, Germany

Johannes C. Reichert, M.D
Queensland University of Technology, 60 Musk Avenue, Kelvin Grove, QLD 4059, Australia

Marcelo N. Rivolta, M.D., Ph.D
Senior Research Fellow, Centre for Stem Cell Biology and Department of Biomedical Sciences, Addison Bldg, Western Bank, University of Sheffield, S10 2TN Sheffield, UK

Joachim Rychly, Ph.D.
Director/Professor, Laboratory of Cell Biology, University of Rostock, Schillingallee 69, Rostock 18057, Germany

Siamak Saifzadeh, DVM, Ph.D
Queensland University of Technology, 60 Musk Avenue,
Kelvin Grove, QLD, 4059, Australia

Virender S. Sangwan, M.D
Prof Brien Holden Eye Research Centre, L.V. Prasad Eye Institute,
Banjara Hills, 500 034 Hyderabad, AP, India

Peter Sartipy, Ph.D
Senior Principal Scientist and Project Manager,
Cellartis AB, Arvid Wallgrens Backe 20, SE-413 46, Göteborg, Sweden

A. Schmidt, Ph.D
Department of Vectorology and Experimental Gene Therapy,
Biomedical Research Center, University of Rostock Medical School,
Schillingallee 69, D-18057 Rostock, Germany

Michael Schmitt, M.D., Ph.D., MHBA
Professor/Head, Stem Cell Transplantation, Department of Internal Medicine III,
University of Rostock, Ernst-Heydemann-Strasse 6, Rostock 18057, Germany

Michael Schroeter, Ph.D
Centre for Biomaterial Development, Institute of Polymer Research, Helmholtz-Zentrum Geesthacht, Kantstrasse 55, Teltow 14513, Germany

Sebastian Sethe, Ph.D
School of Biological and Biomedical Sciences,
Durham University, South Road, Durham, UK

Amar Deep Sharma
Junior Research Group "Stem Cell Biology", Cluster of Excellence REBIRTH,
Hannover Medical School, Carl-Neuberg-Str. 1, 30623 Hannover, Germany

Michael Sittinger, Ph.D
Department of Rheumatology and Clinical Immunology, Tissue Engineering Laboratory and Berlin-Brandenburg Center for Regenerative Therapies,
Charité-Universitätsmedizin Berlin,
Tucholskystrasse 2, Berlin 10117, Germany

Thomas Skutella, M.D
Director/Professor, Institute of Anatomy, Department of Experimental Embryology and Center for Regenerative Biology and Medicine,
University of Tübingen, Österbergstr. 3, Tübingen 72074, Germany

Sajoscha A. Sorrenino, M.D
Department of Nephrology and Hypertension,
Hannover Medical School, Carl-Neuberg-Str. 1, Hannover, Germany

Vasily Stegaev, M.D
Department of Medicine, Institute of Clinical Medicine, Haartmaninkatu 8,
00029 HUS, Finland

Gustav Steinhoff, M.D., Ph.D
Department of Cardiac Surgery, University of Rostock,
Schillingallee 35, 18057 Rostock, Germany

Ioannis Stratos, M.D
Department of Trauma and Reconstructive Surgery,
University of Rostock, Schillingallee 35, Rostock 18057, Germany

Bodo E. Strauer, M.D., FESC, FACC
Professor Emeritus, Department of Cardiology, Pneumology
and Angiology, Heinrich-Heine-University of Düsseldorf,
Moorenstr. 5, 40225 Düsseldorf, Germany

Pei Sun
Zhongguancun Life Science Park, National Institute of Biological Sciences,
7 Science Park Road, Beijing 102206, China

Kazutoshi Takahashi, Ph.D
Lecturer, Center for iPS cell Research and Application, Institute for Integrated
Cell-Material Sciences, Kyoto University, Kyoto 606-8507, Japan

Masayo Takahashi, M.D., Ph.D
Laboratory for Retinal Regeneration, Center for Developmental Biology, RIKEN,
2-2-3 Minatojima-minamimachi, Chuo-ku, Kobe 650-0047, Japan

Minoru Tanaka, Ph.D
Institute of Molecular and Cellular Biosciences,
University of Tokyo, 1-1-1 Yayoi, Bunkyo-ku, Tokyo, Japan

Andre Terzic, M.D., Ph.D
Professor of Medicine and Pharmacology,
Marriott Heart Disease Research Program, Division of Cardiovascular Diseases,
Departments of Medicine, Molecular Pharmacology and Experimental
Therapeutics, and Medical Genetics, Mayo Clinic,
200 First Street SW, Rochester, MN 55905, USA

Bernard Thébaud, M.D., Ph.D
Professor, Department of Pediatrics, Northern Alberta Neonatal Program,
Women and Children's Health Research Institute; Cardio-Vascular Research
Center; Pulmonary Research Group, University of Alberta,
Edmonton, AB, Canada

Veli-Matti Tiainen, Ph.D
ORTON Orthopaedic Hospital, ORTON Foundation,
Tenholantie 10, 00280 Helsinki, Finland

Gudrun Tiedemann, Ph.D
Deputy Head of Reference and Translation Center for Cardiac
Stem Cell Therapy (RTC), University of Rostock,
Schillingallee 68, 18057 Rostock, Germany

Gerben M. van Buul, M.D
Departments of Orthopaedics & Radiology,
University Medical Center Rotterdam,
Molewaterplein 50, 3015 GE, Rotterdam, the Netherlands

Gerjo J.V.M. van Osch, Ph.D
Associate Professor, Departments of Orthopaedics & Otorhinolaryngology,
University Medical Center Rotterdam, Molewaterplein 50, 3015 GE,
Rotterdam, The Netherlands

Geeta K. Vemuganti, M.D., DNB, FNAMS
Head, Member, Program Committee (AP)
Ophthalmic Pathology Laboratory, Head, Sudhakar and Sreekant Ravi Stem Cell Biology Laboratory, Prof Brien Holden Eye Research Centre, L.V. Prasad Eye Institute, Dr Kallam Anji Reddy Campus, L.V. Prasad Marg,
Banjara Hills, Hyderabad, AP, India 500 034

Hanoch Daniel Wagner, Ph.D
Livio Norzi Professorial Chair
Department of Materials and Interfaces,
Weizmann Institute of Science, 76100 Rehovot, Israel

Wolfgang Wagner, M.D., Ph.D
Professor, Helmholtz-Institute for Biomedical
Engineering, Cell Biology, University of Aachen
Medical School, Pauwelsstrasse 20, 52074 Aachen, Germany

Pei Wen
Zhongguancun Life Science Park, National Institute of Biological Sciences,
7 Science Park Road, Beijing 102206, China

Britt Wildemann, Ph.D
Professor, Julius-Wolf Institute, and Berlin-Brandenburg Centre
for Regenerative Therapies, Charité Campus Virchow-Klinikum,
Augustenburger Platz 1, 13353 Berlin, Germany

Patrick Wuchter, M.D
Department of Medicine V, Heidelberg University,
Im Neuenheimer Feld 410, 69120 Heidelberg, Germany

Rongwen Xi, Ph.D
Zhongguancun Life Science Park, National Institute of Biological Sciences,
7 Science Park Road, Beijing 102206, China

Satsuki Yamada, M.D., Ph.D
Instructor of Medicine, Marriott Heart Disease Research Program,
Division of Cardiovascular Diseases, Departments of Medicine, Molecular Pharmacology and Experimental Therapeutics, and Medical Genetics,
Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA

Shinya Yamanaka, M.D., Ph.D
Director of the, Professor, Center for iPS cell Research
and Application, Institute for Integrated Cell-Material Sciences,
Kyoto University, Kyoto 606-8507, Japan
and
Department of Stem Cell Biology, Institute for Frontier Medical Sciences,
Kyoto University, Kyoto 606-8507, Japan
and
Yamanaka iPS Cell Special Project, Japan Science and Technology Agency,
Kawaguchi 332-0012, Japan
and
Gladstone Institute of Cardiovascular Disease, San Francisco, CA 94158, USA

Jie Zhou, Ph.D
Department of Polymer Science and Engineering, Zhejiang University,
No. 38, Zheda Road, Hangzhou 310027, China

Chapter 1
History of Regenerative Medicine

Raymund E. Horch, Laurentiu M. Popescu, and Elias Polykandriotis

Abstract Generation and regeneration as an answer to disease are far from being a new idea. Philosophers, naturalists and scientists were intrigued by the marvels of regeneration seen in nature. By the middle of the nineties life scientists thought we were only a few years away from bioartificial organs grown in a Petri dish. However, by the dawn of the new millennium it became clear that the mechanistic approach dictated by tissue engineering so far, had neglected issues of vascularization. Processes of angiogenesis were central to homeostasis, bioassimilation and biointegration of tissue engineered constructs. Furthermore, the field of tissue engineering had evolved into something vast, encompassing satellite technologies that were becoming separate science sectors. Advances in genetical engineering, stem cell biology, cloning, biomaterials and biomedical devices to name a few, would come to play a major role of their own – tissue engineering had become a part of a bigger whole. Regenerative medicine is the collective field to shelter these technologies "*…that seeks to develop functional cell, tissue, and organ substitutes to repair, replace or enhance biological function that has been lost due to congenital abnormalities, injury, disease, or aging"*

1.1 Introduction

"Those who cannot learn from history are doomed to repeat it", claimed the philosopher G. Santayana in his book "The life of reason" (Santayana 1905). Although this statement reminds somehow of a cliché and its essence is being constantly disputed

R.E. Horch (✉) and E. Polykandriotis
Department of Plastic and Hand Surgery, University of Erlangen, Krankenhausstr. 12, 91054 Erlangen, Germany
e-mail: raymund.horch@uk-erlangen.de

L.M. Popescu
"Victor Babes", National Institute of Pathology, 99-101 Splaiul Independentei, 050096 Bucharest, Romania
and
Department of Cellular and Molecular Medicine, "Carol Davila" University of Medicine and Pharmacy, Bucharest 35, Romania

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Table 1.1 Scientometric data based on Thomson Reuters released information (August 2009)

	Tissue engineering	Regenerative medicine
Total no of PubMed papers (starting in.)	14,517 (since 1988)	2,197 (since 2001)
Year of maximum	–	2008 (ca. 600)
Most cited paper	2,452 citations	1,366 citations
Top 100 papers	At least 200 citations each	At least 40 citations each

through the ages, one could hardly find a better example to report upon, other than the case of regenerative medicine. It is widely admitted that the very term of "Regenerative medicine" was coined to express a need for reorientation (Table 1.1). By the end of the twentieth century, biotechnology firms had maneuvered themselves into a dead-end financially, as well as conceptually (Mason 2007). Furthermore, the field of tissue engineering had evolved into something vast, encompassing satellite technologies that were becoming separate science sectors. Advances in genetical engineering, stem cell biology, cloning, biomaterials and biomedical devices to name a few, would come to play a major role of their own – tissue engineering had become a part of a bigger whole. And it is undisputable that biologicals will be the future (Mason and Dunnill 2008). To quote Paul Kemp: "hype, hubris and hyperbole aside – regenerative medicine will make a real and positive difference…" (Kemp 2006). But where did it all start?

1.2 Regenerative Medicine in the Ancient World

In his *Theogony*, Hesiod (eighth century BC) introduces Prometheus (Fig. 1.1) having created man out of clay and providing him with fire as a source of knowledge. "Hear the sum of the whole matter in the compass of one brief word – every art possessed by man comes from Prometheus" (Aeschylus 415 BC). By doing that, Prometheus had provoked the wrath of Zeus. He had Prometheus carried to Mount Caucasus (or the Carpathian mountains) where an eagle (often mistaken as a vulture) by the name of Ethon would pick at his liver; it would grow back each day and the eagle would eat it again. His torture lasted 30,000 years until he was freed by Hercules (Fig. 1.1). Interestingly enough, the liver is generally speaking the only of the human organs to regenerate itself spontaneously in the case of lesion.[1] The ancient Greeks were well aware of this, hence they named liver (Greek: hēpar, ἠπαρ) after hēpaomai (ηπάομαι), meaning to "repair oneself".

Later on, Aristotle devised two scripts dealing with generation and regeneration in the animal realm. In his "Generation of animals" he related early development with regenerative potential, whereas in "The history of animals" he made observations on

[1]Now the phenomenon of desquamation of the intestinal epithelium and the epidermis has been described. The intestinal epithelium is completely regenerated in 4–5 days. The total regeneration of the epidermis takes 4 weeks. This may mean that for a life expectancy of 77 years, the human epidermis is regenerated 1,000 times.

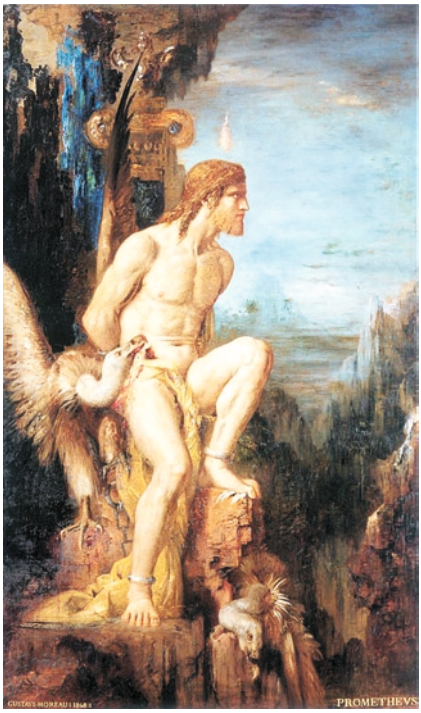

Fig. 1.1 "Prometheus", Gustave Moreau 1868 (Musée Gustave Moreau, Paris). According to some investigators, his torture held for 30,000 years. After having provoked the wrath of Zeus, the eagle Ethon, picked at his liver every night. During the day the liver would regenerate

regeneration on the limb of salamanders and deer antlers Aristotle 1984. He propagated that biological form originates from undifferentiated matter and clearly favoured what would later be described as "epigenesis"(Fig. 1.2).

In the biblical tradition "the Lord God then built up into a woman the rib that he had taken from the man" (Genesis). The quest for tissue replacement was even more graphically demonstrated in the tradition of Cosmas and Damian. Their practice of medicine and surgery in Asia Minor without fee (hence called 'Anagyroi,' without silver) and their martyrdom in Aegea, in Cilicia made a lasting impression upon the early Church. The grafting by these physician-surgeons of a moor's leg in replacement of a patient's diseased leg, and his surprise at finding himself possessed of two sound legs, his own white, and the other black, has been the subject of numerous paintings the majority of which depict the brothers in long robes, holding surgical instruments, boxes of salves, gallipots, or other medical appliances (Matthews 1968) (Fig. 1.3). Graveyards from the Paracas and Parachamac regions in Peru provide ample evidence that pre-Incan surgeons were performing trephination in great numbers as early as 3000 BC. A survey of more than 10,000 mummies from prehistoric Peru demonstrated that roughly 6% showed cranial trephination. There is strong evidence that the occasional cranioplasty was also performed. Trephined

Fig. 1.2 Aristotle's bust. Roman copy from the bronze original by Lyssipos (fifth century BC). (Ludovisi Collection). Aristotle wrote two major works on generation and regeneration in the animal realm. He related early development with regenerative potential and propagated that biological form originates from undifferentiated matter (epigenesis)

Incan skulls have been discovered adjacent to shells, gourds, and silver or gold plates (Asenjo 1963).

1.3 Regeneration in Early Research

Until the middle of the eighteenth century the motive power of biological organisms was thought to be an abstract vital force. Descartes (1596–1650) in his L' Homme postulated that the body works like a machine and biological phenomena are void of a divine meaning but can be explained by means of their physical properties. Lavoisier (1743–1794) postulated further on, that function and viability of organisms depended on chemical processes that could be reproduced in the laboratory. During the same time phenomena of generation and regeneration intrigued scientists and divided them into two distinct camps. Preformationists supported that appendages to be regenerated and organisms to be born pre-existed as miniatures at the site of interest. So, at the base of a severed lizard tail, in their conception a miniature tail was preformed and waited to be "activated" by an amputation. Likewise, in the sperm or in the ovum of the human there existed a miniature "homunculus" that grew into a newborn infant. This theory prevailed until the middle of the eighteenth

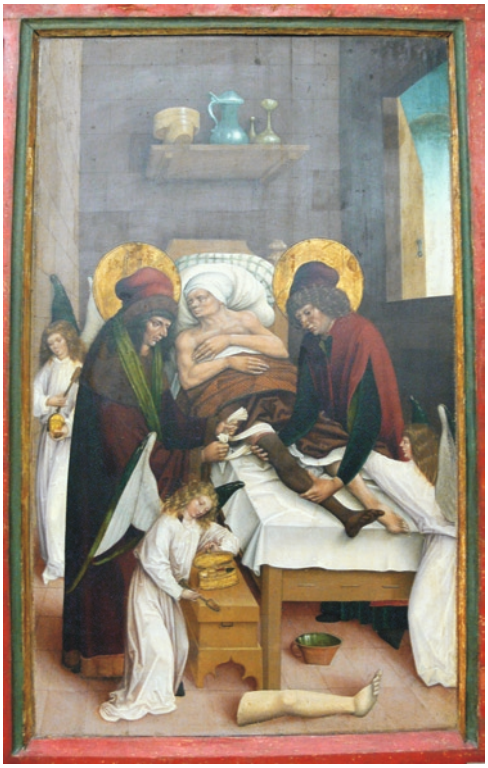

Fig. 1.3 Saints Cosmas and Damian "Transplantation of a leg by Saints Cosmas and Damian, assisted by angels", early sixteenth century (Stuttgart, Germany). According to the tradition of Cosmas and Damian these saints grafted a moors leg as a replacement of a patient's diseased leg

century being concordant with the mechanistic framework provided at the time and did not come into a direct conflict with the Christian beliefs about divine involvement in the processes of life. On the contrasting end, came the Aristotelean thesis that undifferentiated matter was able to give rise to life. This theory had been actually named "epigenesis" by William Harvey (1578–1657) in his work "on the generation of animals" grossly repeating on Aristotle's works.

In the eighteenth century the process of regeneration in amphibians was matter of intense study. Abraham Trembley (1710–1784) produced several publications on the regenerative phenomena on freshwater polyps. He managed to obtain a clone of 50 polyps from one organism that he had quartered. He performed sections at every conceivable plane, contradicting preformational beliefs of the time (Dinsmore 1991). The question was posed: If the animal soul was the organizing and unifying element of life, how could a newly regenerated form arise? Reaumer and Spallanzani reported about their studies on crustaceans and salamanders respectively (Dinsmore 1991).The latter, being a great methodologist, expanded his research on a number of different organisms including frogs, toads, slugs and snails. He published his