Edited by Felix Kratz, Peter Senter
and Henning Steinhagen

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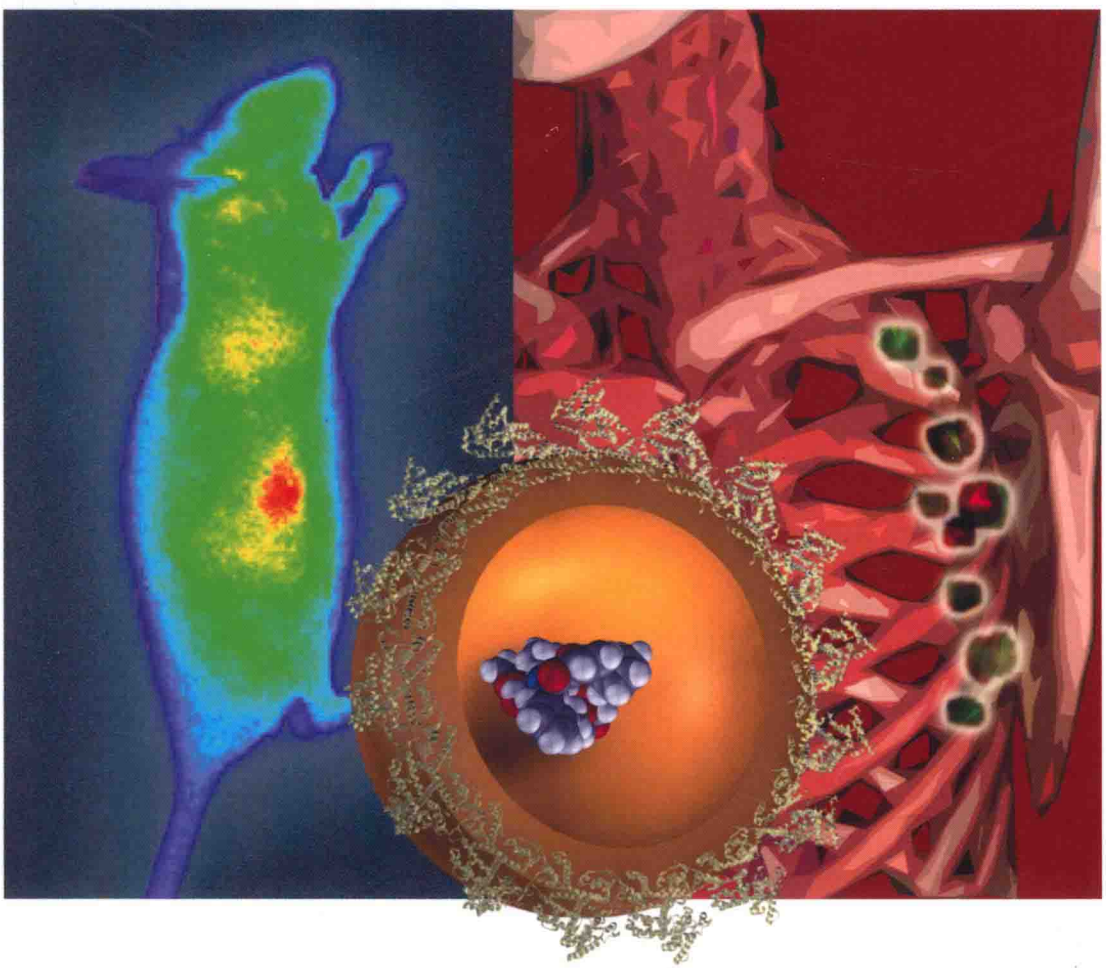
Drug Delivery in Oncology

From Basic Research to Cancer Therapy

Volume 1



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The Editors

Dr. Felix Kratz
Head of the Division of
Macromolecular Prodrugs
Tumor Biology Center
Breisacherstrasse 117
D-79106 Freiburg
Germany

Dr. Peter Senter
Vice President Chemistry
Seattle Genetics, Inc.
218, Drive S.E. Bothell
Seattle, WA 98021
USA

Dr. Henning Steinhagen
Vice President
Head of Global Drug Discovery
Grünenthal GmbH
Zieglerstr. 6
52078 Aachen
Germany

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Foreword

It is highly likely that the reason our therapies so often fail our patients with cancer is that either (i) those therapies actually never get to their intended targets or (ii) those therapies are "intercepted" by similar targets on normal cells. If we want to understand why many of our therapies fail our patients, and what we can do to possibly remedy those failures, this book *Drug Delivery in Oncology* can help all of us achieve that understanding – and with this book it will be a state-of-the-art understanding.

Drs. Kratz, Senter, and Steinhagen have assembled a respectable breadth of both seasoned and precocious investigators to put together this very special treatise (49 chapters in all). The chapters are well written with basic science, preclinical, and clinical perspectives.

The book begins with a history and the limitations of conventional chemotherapy. Expert discussions of the vascular physiology of tumors that affect drug delivery (and how to defeat those issues) then follow. There are excellent discussions of the neonatal Fc receptor, development of cancer targeted ligands, and antibody-directed enzyme prodrug therapy (ADEPT).

A very special part of this book is the emphasis on tumor imaging. Again, the authors are major experts in this field, which undoubtedly will continue to mature to enable us to document whether or not our therapeutics actually make it to their intended target(s) – and if not, why not.

There are impressive chapters on macromolecular drug delivery systems, including biospecific antibodies, antibody–drug conjugates, and antibody–radionuclide conjugates. Up-to-date discussions of polymer-based drug delivery systems including PEGylation, thermoresponsive polysaccharide-based and even low-density lipoprotein–drug complexes are also presented.

Those with an interest in learning about nano- and microparticulate drug delivery systems can study liposomes to immunoliposomes, to hydrogels, micelles, albumin–drug nanoparticles, and even carbon nanotubes, which are all covered in this book.

Other special delivery systems covered include peptides–drug conjugates, vitamin–drug conjugates, and growth factor–drug conjugates, conjugates of drugs with fatty acids, RNA and RNA interference delivery, and specific targeted organ drug delivery.

As investigators who want to more effectively treat and indeed cure cancer we have many worries. The first of these is that many of our therapeutics just do not make it into the targets in the tumors. This book gives the reader a comprehensive insight into multiple ways to address this problem. A second major worry is that we are losing our pharmacologists who can solve those drug delivery issues. The editors and the authors of this incredible treatise give us comfort that these pharmacologists are alive and well, and thinking as to how they can contribute to getting control of this awful disease.

Daniel D. Von Hoff, MD, FACP
Physician in Chief and Distinguished Professor,
Translational Genomics Research Institute (TGen)
Professor of Medicine, Mayo Clinic
Chief Scientific Officer, Scottsdale Healthcare and US Oncology

Preface

Modern oncology research is highly multidisciplinary, involving scientists from a wide array of specialties focused on both basic and applied areas of research. While significant therapeutic advancements have been made, there remains a great need for further progress in treating almost all of the most prevalent forms of cancer. Unlike many other diseases, cancer is commonly characterized by barriers to penetration, heterogeneity, genetic instability, and drug resistance. Coupled with the fact that successful treatment requires elimination of malignant cells that are very closely related to normal cells within the body, cancer therapy remains one of the greatest challenges in modern medicine.

Early on, chemotherapeutic drugs were renowned for their systemic toxicities, since they poorly distinguished tumor cells from normal cells. It became apparent to scientists within the field that further advancements in cancer medicine would require new-generation drugs that ideally targeted critical pathways, unique markers, and distinguishing physiological traits that were selectively found within the malignant cells and solid tumor masses. Several new areas of research evolved from this realization, including macromolecular-based therapies that exploit impaired lymphatic drainage often associated with solid tumors, antiangiogenesis research to cut the blood supply off from growing tumors, antibody-based strategies that allow for selective targeting to tumor-associated antigens, and new drug classes that attack uniquely critical pathways that promote and sustain tumor growth. A large proportion of both recently approved and clinically advanced anticancer drugs fall within these categories.

Beyond the generation of such drug classes, it has also been recognized that approved cancer drugs could be made more effective and less toxic through delivery and transport technologies that maximize tumor exposure while sparing normal tissues from chemotherapeutic damage. By doing so, existing or highly potent cytotoxic drugs may display improved therapeutic indices. This has attracted considerable attention and has spawned the area of macromolecular-based delivery strategies.

There are few places where those actively engaged in drug delivery or who may wish to enter the field can find the major advancements consolidated in one place. This prompted us to organize the series of books entitled *Drug Delivery in Oncology* comprised of 49 chapters written by 121 internationally recognized

leaders in the field. The work within the book series overviews many of the major breakthroughs in cancer medicine made in the last 10–15 years and features many of the chemotherapeutics of the future. Included among them are recombinant antibodies, antibody fragments, and antibody fusion proteins as well as tumor-seeking ligands for selective drug delivery and tumor imaging, and passive targeting strategies using macromolecules and nano- and microparticulate systems.

One of the special distinguishing features of this series is that the chapters are written for novices and experts alike. Each chapter is written in a style that allows interested readers to not only to find out about the most recent advancements within the field being discussed, but to actually see the data in numerous illustrations, photos, graphs, and tables that accompany each chapter.

None of this would have been possible without the devoted efforts of the contributing authors, all of whom shared the common goal of creating a new series of books that would provide an important cornerstone in the modern chemotherapeutic treatment of cancer. We are all very thankful for their efforts.

We also wish to thank the publishing team at Wiley-VCH in Weinheim, Germany. In particular, we want to give our wholehearted thanks and kind acknowledgments to Frank Weinreich, Gudrun Walter, Bernadette Gmeiner, Claudia Nußbeck, Hans-Jochen Schmitt, and Ina Wiedemann, who were always helpful and supportive during the 2 years it took to put all this together. It is our hope that this series will provide readers with inspired ideas and new directions for research in drug delivery in oncology.

July 2011

Felix Kratz
Peter Senter
Henning Steinhagen

List of Contributors

Khalid Abu Ajaj received his BSc from Yarmouk University (Jordan, 1991), his MSc from the University of Jordan (Jordan, 1995), and his PhD in Chemistry from the University of Leipzig (Germany, 2002). He then carried out a Postdoctoral Fellowship in the research groups of Professor Dr. A. Zychlinsky (Max Planck Institute for Infection Biology, Berlin) and Professor Dr. M. Bienert (Institute of Molecular Pharmacology, Berlin), developing bacterial lipopeptides to investigate the mechanisms of activation of Toll-like receptors. He joined the Macromolecular Prodrug Research Group of Dr. Felix Kratz at the Tumor Biology Center in Freiburg in 2006. His research in the group is focused on developing dual-acting prodrugs for circumventing multidrug resistance.

Stephen C. Alley received his PhD in Organic Chemistry from the University of Washington and completed a Postdoctoral Fellowship in Chemistry at Pennsylvania State University. He joined the Research Biology Department at Pathogenesis Corp. and then came to Seattle Genetics in 2003. His research has surrounded conjugation technologies and determination of the mechanisms by which antibody–drug conjugates work.

Jan Terje Andersen graduated in Molecular Immunology at the Department of Molecular Biosciences, University of Oslo, Norway in 2008. He has a postdoctoral position at the Department of Molecular Biosciences, University of Oslo, and the Center for Immune Regulation at the Institute for Immunology, Norway. His research areas are molecular biology and immunology, with a current focus on receptor interactions and receptor targeting. Specifically, the interactions of antibodies of the IgG class with the Fcγ receptors as well

as the interactions of IgG and albumin with the neonatal Fc receptor. He has authored approximately 15 scientific publications, including book chapters and patent applications.

Christopher Bachran studied Biochemistry at the Freie Universität Berlin, Germany. He joined the laboratory of Hendrik Fuchs at the Charité–Universitätsmedizin Berlin as a PhD student to study targeted protein toxins for targeted tumor therapy in 2002 and obtained his PhD from the Freie Universität Berlin in 2006. He stayed in Hendrik Fuchs' group as postdoc to investigate the efficacy of saporin-based targeted toxins in mouse models and to analyze the impact of saponins for drastically improved drug delivery in tumor mouse models. During this time he co-organized with Hendrik Fuchs the 2nd and 4th Fabisch-Symposium for Cancer Research and Molecular Cell Biology on the topic of targeted tumor therapies in 2006 and 2009. In 2009, he joined the laboratory of Stephen Leppla at the National Institute of Allergy and Infectious Diseases, National Institutes of Health, in order to develop sophisticated anthrax toxin-based targeted tumor therapy approaches.

You Han Bae received his PhD degree in Pharmaceutics from the University of Utah in 1988, and has held a Full Professorship at the Department of Pharmaceutics and Pharmaceutical Chemistry of University of Utah since 2002. His research interests include self-assembled superintelligent nanoparticulates for multidrug-resistant tumors, acidic solid tumor targeting, protein drug stabilization and controlled release, polymeric vector design for genetic materials, and polymeric systems for rechargeable cell delivery. He has authored over 210 peer-reviewed scientific publications, book chapters, and US patents.

Kenneth D. Bagshawe is Emeritus Professor of Medical Oncology at Imperial College London. After service in the Royal Navy, he studied medicine at St. Mary's Hospital Medical School in London. He was a Research Fellow at Johns Hopkins Hospital Baltimore. He reported first use of combination chemotherapy resulting in cure of metastatic cancer. He established the first radioimmunoassay for human chorionic gonadotropin. He set up a national-scale registration scheme for patients with hydatidiform mole in 1973. He was Chairman of the Scientific Committee of the Cancer Research Campaign. He proposed ADEPT in 1987 and 1990, carried out the first clinical trial of ADEPT. He is a Fellow of the Royal Society.

Ambros Beer studied Medicine at the Ludwig-Maximilians-Universiät in Munich, Germany. After his final exam in 1999, he performed his training in Radiology at the Department of Radiology at the Klinikum rechts der Isar of the Technical University in Munich (Professor Dr. E.J. Rummeny). Afterwards he performed his training in Nuclear Medicine at the Department of Nuclear Medicine at the Klinikum rechts der Isar of the Technical University in Munich (Professor Dr. M. Schwaiger). Currently he is working as Attending and Assistant professor at the Department of Nuclear Medicine at the Klinikum rechts der Isar of the Technical University in Munich. His main research interest is translational molecular imaging, with a focus on assessment of angiogenesis using targeted tracers, like $\alpha_v\beta_3$-specific tracers. Moreover, he is interested in multimodality molecular imaging, combining, for example, magnetic resonance imaging and positron emission tomography.

Elvin Blanco received his BS in Biomedical Engineering from Case Western Reserve University in Cleveland, OH. He received his PhD in Biomedical Engineering under the mentorship of Dr. Jinming Gao at the University of Texas Southwestern Medical Center at Dallas in 2008. In 2009, he began his postdoctoral training under the mentorship of Dr. Mauro Ferrari at the University of Texas Health Science Center at Houston. He is currently a Research Associate at the Methodist Hospital Research Institute in Houston under the mentorship of Dr. Mauro Ferrari.

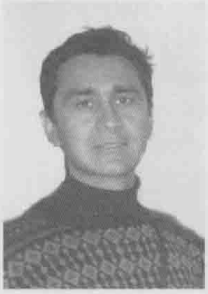
Andreas K. Buck graduated in Medicine at the University of Ulm, Germany in 1996. From 1997 to 2003 he worked as a Resident and from 2003 to 2006 as a Senior Physician at the Department of Nuclear Medicine at the University of Ulm. From 2006 to 2010 he worked as Associate Professor at the Department of Nuclear Medicine at the Technical University in Munich, Germany. Since 2011 he has been Director of the Department of Nuclear Medicine at the University of Wuerzburg, Germany. His research is focused on hemato-oncology and cancer treatment with radiopharmaceuticals.

Horacio Cabral received his PhD under the supervision of Professor K. Kataoka in Materials Engineering from the University of Tokyo in 2007. He worked as an Assistant Professor at the Division of Clinical Biotechnology, Graduate School of Medicine, University of Tokyo until 2009. From 2010, he has been a Lecturer at the Bioengineering Department, University of Tokyo. His main research interests relate to smart nanodevices for the diagnosis and therapy of cancer.

Marcelo Calderón received his PhD in Organic Chemistry in 2007 from the National University of Córdoba, Argentina, under the supervision of Professor Miriam Strumia. In the following years, he joined the Research Group of Professor Rainer Haag at the Free University of Berlin as a Postdoctoral Fellow. He is currently working as an Associate Researcher at the same University, with a research interest in the development of nanotransporters based on dendritic polyglycerol for intelligent delivery of drugs, gene, and imaging probes.

John C. Chang MD, PhD graduated from the University of Illinois at Urbana-Champaign with an MD and an Electrical Engineering PhD degree in 2004. During his graduate training, he has authored and coauthored five refereed articles focused on neural engineering. During his radiology residency at Stanford University, he pursued research in nanoparticle application in optical and magnetic resonance imaging with ultimate application in understanding cancer biology and novel therapy. He currently serves as a Clinical Instructor in Radiology at Stanford University.

Coralie Deladriere studied Chemistry at the University Paris Sud (France) and obtained her Master's degree in Analytical Chemistry in 2006. She then joined the Polymer Therapeutics Laboratory headed by Dr. Vicent at the Centro de Investigación Príncipe Felipe, Valencia (Spain) as a PhD Student. Her PhD work is focused on the development of polymer–drug conjugates as a platform for combination therapy in the treatment of hormone-dependent breast cancer.

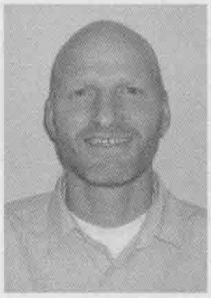


Neil Desai is currently Senior Vice President of Global Research and Development at Abraxis BioScience in Los Angeles, CA, where he is responsible for the development of the company's growing product pipeline and the development of the company's intellectual property portfolio. He is an inventor of ABI's nanotechnology and nanoparticle-albumin bound (*nab*™) drug delivery platform, and was primarily responsible for the development of its nanotechnology drug *nab*-paclitaxel and the discovery of the novel targeted biological pathway utilized by *nab*-drugs. Prior to joining ABI, he was Senior Director of Biopolymer Research at VivoRx Inc., where he developed novel encapsulation systems for living cells and was part of the team that performed the world's first successful encapsulated islet cell transplant in a diabetic patient. With more than 20 years of experience in the research and development of novel drug delivery systems and biocompatible polymers, he holds over 100 issued patents and peer-reviewed publications, has made over 150 presentations at scientific meetings, and has organized and chaired symposia in the areas of biocompatible polymers and nanotechnology-based delivery systems. He is a reviewer for several scientific journals, and an active participant in the US Food and Drug Administration (FDA) Nanotechnology Task Force and FDA-Alliance for Nanohealth initiatives. He holds a MS and PhD in Chemical Engineering from the University of Texas at Austin, USA, and a BS in Chemical Engineering from the University Institute of Chemical Technology in Mumbai, India.

Laurent Ducry studied Chemistry at the University of Lausanne (Switzerland) and did his Diploma thesis with Professor T. Gallagher at the University of Bristol (UK). He obtained his PhD from the ETH Zürich (Switzerland) with Professor F. Diederich in 1998. During his graduate studies, he worked for 6 months with Dr. G. Olson at Hoffmann-La Roche in Nutley (New Jersey). He then held a Swiss National Science Foundation Postdoctoral Fellowship at the University of Pennsylvania in Philadelphia with Professor A.B. Smith III and Professor R. Hirschmann. He began his industrial carrier in process R&D at Lonza in Visp (Switzerland) in 2000 and became Project Leader the following year. His activities focused on the development and scale-up of chemical processes, as well as the production of pharmaceutical intermediates and active pharmaceutical ingredients under current Good Manufacturing Practices. In the second half of 2006 he trained the Lonza R&D team in Nansha (China) and was promoted to Senior Research Associate in 2007. Since 2008, he has been leading the antibody–drug conjugates R&D group of Lonza.

Anat Eldar-Boock is currently undertaking her PhD studies at Tel Aviv University under the supervision of Dr Ronit Satchi-Fainaro. Her thesis goal is to synthesize and characterize antiangiogenic and anticancer polymer therapeutics bearing paclitaxel and RGD peptidomimetics for the treatment of breast cancer. She graduated her MS studies from Tel Aviv University at the Department of Developmental Biology investigating the involvement of sphingolipid metabolism in aging and apoptosis of rat oocytes.

Bakheet Elsadek graduated in Pharmaceutical Sciences from Al-Azhar University, Egypt in 2001. He was then awarded the Master's degree in Biochemistry from the Faculty of Pharmacy, Assiut University, Egypt. In 2010 he received his PhD from the Faculty of Pharmacy, Assiut University, supervised by Dr. Felix Kratz, Head of the Division of Macromolecular Prodrugs, Clinical Research, Tumor Biology Center, Freiburg, Germany and Professor Dr. Tahia Saleem, Professor of Biochemistry and Molecular Biology, Faculty of Medicine, Assiut University. His PhD thesis was funded through the Egyptian Scientific Channel System and focused on the development of prodrugs for treating prostate cancer. His current research areas are angiogenesis, drug targeting, and drug delivery systems in oncology and prodrugs.



Hans Erickson received his PhD in Biochemistry from the University of California, San Diego. After a Postdoctoral Fellowship at the University of Utah, he joined ImmunoGen, Inc., where his efforts have focused on understanding the mechanisms associated with the efficacy and toxicity of antibody–drug conjugates.

Freddie Escorcia is a MD PhD candidate at the Weill Cornell/Rockefeller/Sloan-Kettering Tri-Institutional Program. He has a BS in Chemistry and Bioengineering from the University of Illinois. His research interests are in understanding the mechanisms of action and therapeutic applications for targeting of tumor vasculature and tumor angiogenesis.

Omid C. Farokhzad received his MD and MA from Boston University School of Medicine. He completed his postdoctoral clinical and research training at Brigham and Women's Hospital/Harvard Medical School (HMS) and MIT in the laboratory of Professor Robert Langer. He is an Associate Professor at HMS, and directs the Laboratory of Nanomedicine and Biomaterials at Brigham and Women's Hospital. He pioneered the development of aptamer–nanoparticle conjugates for cancer therapy. His laboratory is currently focused on the high-throughput screening of targeting ligands and the development of multifunctional targeted nanoparticle platforms for medical applications.

Henry Fechner studied Veterinary Medicine at the Humboldt University of Berlin and received his DVM in 1995 at the Free University of Berlin in the Institute of Virology. He then worked as an assistant in the Institute of Veterinary Pathology in the Free University of Berlin and as a postdoc in the "Lipidlabor" of the Charité Berlin from 1996 to 1998. From 1998 to 2010 he was postdoc and group leader in the Department of Cardiology and Pneumology of the Charité Berlin. In 2010 he received a senior group leader position at the University of Berlin in the Institute of Biotechnology. His research interests focus on the development of gene therapeutic strategies for the treatment of cardiovascular and tumor diseases.

Mauro Ferrari obtained his Dottore in Mathematics from Università di Padova in Italy and received his PhD in Mechanical Engineering from the University of California at Berkeley. From 2003 to 2005, he served as an Expert on Nanotechnology at the National Cancer Institute (NCI), providing leadership into the formulation, refinement, and approval of the NCI's Alliance for Nanotechnology in Cancer. Currently, he is the President, CEO, and Director of the Methodist Research Institute, Ernest Cockrell Jr. Endowed Chair, and President of the Alliance for NanoHealth in Houston, TX.

Efrén J. Flores MD received his medical degree at the University of Puerto Rico School of Medicine in 2005 and completed his Residency in Diagnostic Radiology at Massachusetts General Hospital in 2010. His relationship with Dr. Mukesh Harisinghani as a mentor has allowed him to developed a new interest in the future impact of magnetic nanoparticles in cancer treatment.

Gert Fricker graduated in Chemistry from the University of Freiburg, Germany in 1986. He then did postdoctoral research at the Department of Clinical Pharmacology, University Hospital Zurich, Switzerland. From 1888 to 1995, he worked as a Research Scientist at Sandoz, Basle, Switzerland. In 1995, he was appointed Professor of Pharmaceutical Technology and Biopharmacy at the University of Heidelberg, Germany. Since 2002 he has been Director of the Institute of Pharmacy and Molecular Biotechnology at the University of Heidelberg and the Steinbeis Technology Transfer Center Biopharmacy and Analytics. His research interests include drug delivery, membrane transport proteins, and the blood–brain barrier.

Jillian H. Frieder earned her Bachelor in Physiology from the University of Arizona in 2010. In July 2010 she joined Professor Omid Farokhzad's group at Brigham and Women's Hospital. Her current work involves aptamer–nanoparticle targeting for *in vivo* applications.

Hendrik Fuchs studied Biochemistry at the Freie Universität Berlin, Germany, and finished his PhD work on the human transferrin receptor in 1996 in the laboratory of Reinhard Geßner. After a short postdoc at the Rudolf Virchow University Hospital in Berlin, he became a group leader in 1997 at the Department for Clinical Chemistry and Pathobiochemistry, headed by Rudolf Tauber, at the Benjamin Franklin University Hospital in the same city. Since that time his research focus is on the investigation of systemic and cellular iron metabolism and on the development of protein-based targeted antitumor drugs. After his habilitation in 2002 he continued his research as a German Privatdozent and was appointed as Professor at the Department of Laboratory Medicine, Clinical Chemistry and Pathobiochemistry at the Charitè–Universitätsmedizin Berlin in 2010. He organized together with Christopher Bachran the 2nd and 4th Fabisch-Symposium for Cancer Research and Molecular Cell Biology on the topic of targeted tumor therapies in 2006 and 2009.