Edited by Claus Jacob,
and Paul G. Winyard

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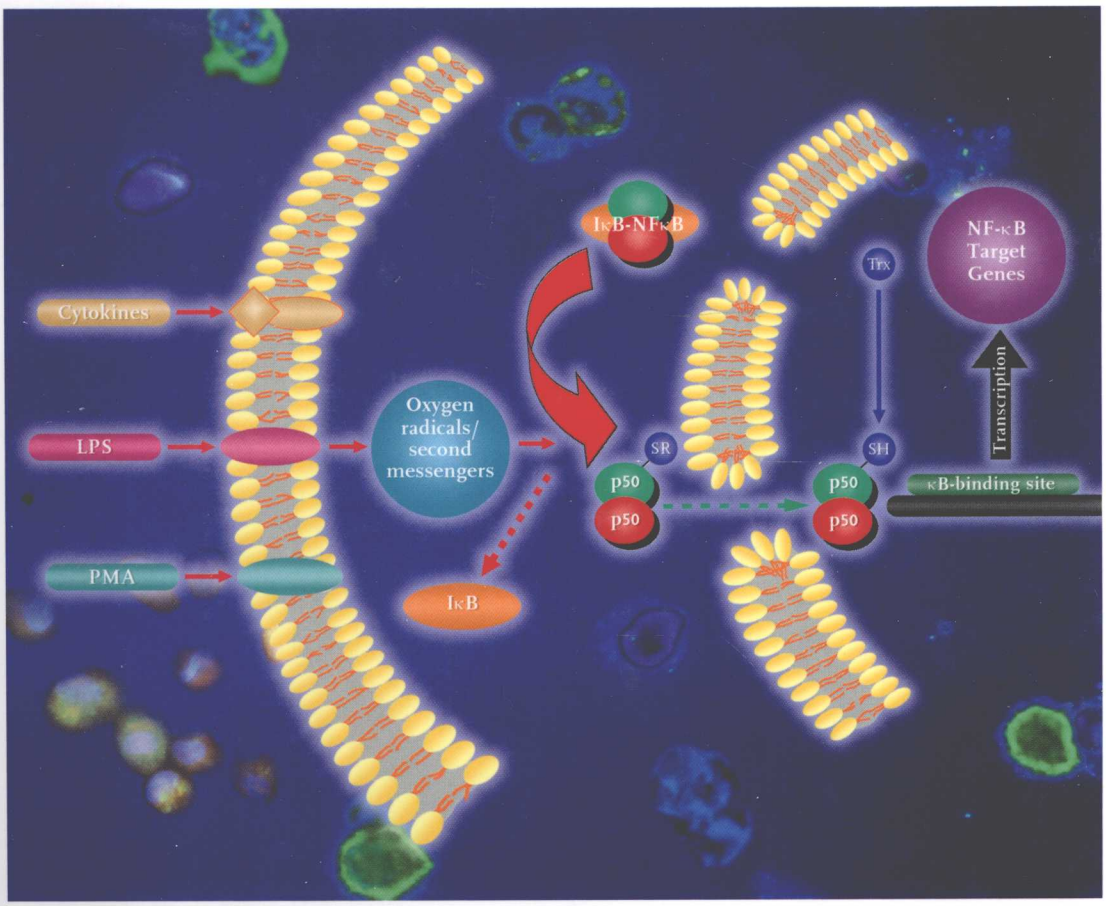
Redox Signaling and Regulation in Biology and Medicine



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The Editors

Jun. -Prof. Dr. Claus Jacob
Universität des Saarlandes
Bioorgan. Chemie-Geb.B21
Campus
66123 Saarbrücken

Prof. Dr. Paul G. Winyard
University of Exeter
Biomedical & Clinical Science
St. Luke's Campus
Exeter EX1 2LU
United Kingdom

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Preface

During the last decade, the area of intracellular redox processes, signaling and control has witnessed many remarkable developments. Discoveries such as the widespread occurrence of highly oxidized cysteine residues in proteins, sulfiredoxin, sulfinic acid switches in peroxiredoxins, widespread glutathiolation in proteins, redox-controlled chaperone activity, redox-regulated transcription factor activation, antioxidant response networks and redox-controlled apoptotic pathways, have resulted in a wealth of new knowledge. At the same time, the significance of redox control has been further underlined by the emerging links between cellular redox events and many human illnesses, as well as an apparent connection between oxidative stress and aging.

Many of these developments have been the focus of recent scientific meetings, such as the 2006 Mosbach Kolloquium in Germany ("Redox Signaling: Mechanisms and biological impact") and a high profile Gordon Conference in the USA in June 2006 ("Thiol-based redox regulation & signaling"). There are also a number of excellent reviews, some of which have been authored by the contributors of this book, which focus on individual issues of intracellular redox events, for instance oxidative stress, biological sulfur chemistry, intracellular redox pathways, apoptosis and aging. Considering the present literature, various outstanding books are available, which touch on aspects of cellular redox control, such as free radicals or cellular signaling pathways. To date, no appropriate book exists, however, which covers the highly multidisciplinary topics of intracellular redox events in a comprehensive approach – and, at the same time, is accessible to students and cutting-edge researchers alike.

The purpose of this book is therefore four-fold. First, it aims to provide an up-to-date text that covers the range of recent developments in the area of redox signaling and control. The topics covered will, of course, represent a fine selection of key issues only, without any claims to complete coverage of this rather extensive area of research. Here, it is hoped that the themes covered will ultimately stimulate further reading, and plenty of references are provided throughout to guide the search for literature. Second, the book aims at a deeper understanding of redox signaling and control events by taking a holistic, cross-discipline approach which combines the

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various chemical, analytical, biochemical, biological and medical aspects relevant to redox signaling. In doing so, the book hopes to fulfil its third purpose – to provide an easy-to-understand text which can be used by research students, postdoctoral fellows and experienced researchers alike. Here, we have added a set of Explanatory Boxes to each chapter which will provide a basic, easy-to-understand background for some of the more complicated or specialized concepts discussed. While these boxes are designed to assist readers in the first instance, they should not been seen as comprehensive coverage of a particular topic and cannot replace more solid background reading. Last but not least, we hope to provide a book for chemists, biochemists, biologists, oxidative stress and aging researchers that is educational, stimulating and interesting to read.

We would like to thank all of our colleagues who have walked with us on this project, all leading researchers in their fields – without their contributions this book would not, of course, have been possible. Special thanks also go to Wiley-VCH, and in particular to Ms. Stefanie Volk and Dr. Frank Weinreich, for their continuous support, help, advice and above all patience with this book.

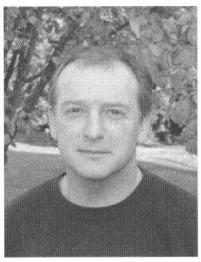
Saarbrücken and Exeter
August 2008

Claus Jacob and Paul Winyard

The Editors

Claus Jacob is Junior Professor of Bioorganic Chemistry at the School of Pharmacy, University of Saarland, Germany. He studied chemistry in Kaiserslautern, Germany, and Leicester, UK, subsequently earning his doctorate from the University of Oxford. From 1996 until 1999 he was a postdoc under Prof. Bert Vallee at Harvard Medical School, before taking up the position of lecturer in inorganic chemistry at the University of Exeter, where he remained until moving to his current position in 2005. Dr. Jacob is currently coordinator of the EU Framework 7 Marie Curie Initial Training Network on "Natural Products and related Redox Catalysts: Basic Research and Applications in Medicine and Agriculture". His particular interest is in the chemistry underlying biochemical redox events, most notably reactive sulfur species.

Claus Jacob, Universität des Saarlandes, School of Pharmacy, Division of Bioorganic Chemistry, 66041 Saarbrücken, Germany



Paul G. Winyard has been Professor of Experimental Medicine at Peninsula College of Medicine and Dentistry, Exeter, UK, since 2002. He previously held a chair in experimental medicine at St Bartholomew's and the Royal London School of Medicine and Dentistry, London, UK, and was a visiting professor at the University of California, San Francisco, from 2000 to 2001. Professor Winyard's research interests center on the role of oxidative/nitrosative stress in such chronic inflammatory diseases as rheumatoid arthritis, with a particular focus on the development of novel therapeutic strategies and free radical assays, as well as the translation of these developments into pre-clinical and early-phase clinical studies.

Paul G. Winyard, Universities of Exeter and Plymouth, Peninsula Medical School, St Luke's Campus, Exeter EX1 2LU, UK

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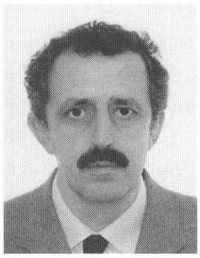
List of Authors



Gustavo Barja obtained his PhD in biological sciences from the Complutense University of Madrid in 1981. He continued his scientific research, performing short stays at the Universities of Paris VII (France), UCLA (USA), Brescia (Italy) and ETH (Switzerland). He has dedicated his research activities to the study of free radicals and oxidative stress in animals, focusing on aging and longevity. He is currently full professor of physiology at Complutense University, where he teaches comparative animal physiology to biology students, as well as PhD courses on comparative biochemistry and aging. He has published three books and over 150 peer-reviewed papers, has participated in 17 multiyear national or international research projects, and has received five prizes for his research into aging, including the Pfizer Foundation Award in 2000. In 2001 he was nominated as a member of the Royal Academy of Pharmacy of Spain.

Gustavo Barja, Complutense University, Faculty of Biology, Department of Animal Physiology-II, Madrid 28040, Spain

Torsten Burkholz studied chemistry at the University of Saarland, Saarbruecken, Germany. He obtained his first degree in chemistry in June 2006. In October 2006, he joined the Division of Bioorganic Chemistry and is currently conducting research as part of his PhD thesis entitled "Oxidative stress and electrochemical procedures for surface decontamination in dialysis". This project is supported by Fresenius Medical Care, Bad Homburg, Germany.

Torsten Burkholz, Universität des Saarlandes, School of Pharmacy, Division of Bioorganic Chemistry, 66041 Saarbrücken, Germany

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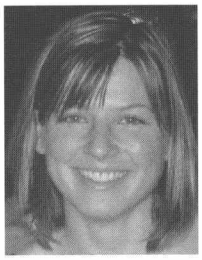
Adam J. Case is a fifth-year combined MD/PhD student at the University of Iowa. He is currently pursing a PhD in free radical and radiation biology, and his research interests include elucidation of the role of antioxidant enzymes in cancer, epigenetics of regulatory enzymes, and the use of antidiabetes medication in the prevention of oncogenesis. Following his thesis dissertation, Adam plans to pursue a medical residency in pediatrics where he hopes to practice both clinical and research medicine in the field of pediatric oncology.

Adam J. Case, The University of Iowa, Holden Comprehensive Cancer Center, Carver College of Medicine, Department of Radiation Oncology, Iowa City, IA 52242-1181, USA



Edith Charlier is a PhD student at the GIGA-Research Center, Liège, Belgium, in the division of Jacques Piette in the subgroup of Geoffrey Gloire. She studied biochemistry at the University of Liège and she joined the division of Jacques Piette for her thesis. She is working on an inositol phosphatase which influences the sensitivity of T lymphocytes to CD95-induced cell death.

Edith Charlier, University of Liège, Virology-Immunology Unit, GIGA-Research, 1, avenue de l'Hopital, 4000 Liège, Belgium

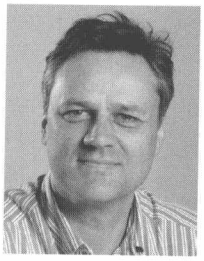
Silvia Cristofanon received her PhD from the University of Rome Tor Vergata in spring 2008 after three years of research at the LBMCC Lab in Luxembourg. Her major interests are related to apototic cell signaling pathways in human leukemia cells induced by glutathione depletion.

Silvia Cristofanon, Hôpital Kirchberg, Fondation Recherche sur le Cancer et les Maladies du Sang, Laboratoire de Biologie Moléculaire et Cellulaire du Cancer (LBMCC), 9, rue Edward Steichen, 2540 Luxembourg and Universita' di Roma "Tor Vergata", Dipartimento di Biologia, via Ricerca Scientifica, 00133 Roma, Italy

Alison Curnow As medical research director of Cornwall Dermatology Research (Peninsula Medical School, UK), Alison Curnow has established one of the top dermatological photodynamic therapy groups in the UK. The clinical and experimental research program aims to improve the effectiveness and diversify the application of this noninvasive light-mediated treatment modality. In addition, the laboratory also investigates the causation and potential prevention of skin carcinogenesis.

She is currently active in undergraduate teaching and postgraduate supervision, as well as being a director of the International Photodynamic Association Board, and has numerous peer-reviewed publications in international scientific and clinical journals to her name.

Alison Curnow, Cornwall Dermatology Research, Peninsula Medical School, The Knowledge Spa, Truro, Cornwall TR1 3HD, UK

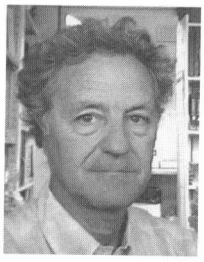


Jeroen den Hertog received his PhD at Utrecht University in 1992, based on a thesis that he prepared at the Hubrecht Laboratory, Netherlands Institute for Developmental Biology. He carried out his postdoc under Tony Hunter at the Salk Institute, La Jolla, CA, USA, from 1992 to 1994. In 1994 he became project leader at the Hubrecht Laboratory and in 1997 group leader, while also being appointed professor of molecular developmental zoology at the University of Leiden in 2008. Dr den Hertog has over 70 scientific publications to his name and is the recipient of several grants from the Dutch Cancer Society, Netherlands Organization for Scientific Research, Netherlands Proteomics Centre and the European Commission. His research interest is the role of tyrosine phosphorylation and dephosphorylation in development and disease.

Jeroen den Hertog, Hubrecht Institute, Uppsalalaan 8, 3584 CT Utrecht, The Netherlands

Mario Dicato is head of Internal Medicine and of the Service of Haematology-Oncology at Luxembourg Medical Centre. Much of his postgraduate training was spent at the University of Pittsburgh, Pittsburgh, Pennsylvania, USA and at Harvard University, Boston, Massachusetts, USA.

Mario Dicato, Hôpital Kirchberg, Fondation Recherche sur le Cancer et les Maladies du Sang, Laboratoire de Biologie Moléculaire et Cellulaire du Cancer (LBMCC), 9, rue Edward Steichen, 2540 Luxembourg, Luxembourg



Paolo Di Simplicio is professor of pharmacology at the University of Siena. His research interest is focused on the functional antioxidant aspects of glutathione and other thiols with special emphasis on the regulation of the redox state of biological systems.

Paolo Di Simplicio, University of Siena, Department of Neuroscience, Pharmacology Unit, 53100 Siena, Italy

Marc Diederich received his PhD in molecular pharmacology in 1994 at the University of Nancy (France). He is currently leading the Laboratoire de Biologie Moléculaire et Cellulaire du Cancer (LBMCC) in Luxembourg. Research in this laboratory is mainly focused on the inhibition of glutathione-based drug resistance mechanism by natural compounds as well as erythroid differentiation mechanisms.

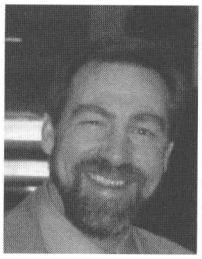
Marc Diederich, Hôpital Kirchberg, Fondation Recherche sur le Cancer et les Maladies du Sang, Laboratoire de Biologie Moléculaire et Cellulaire du Cancer (LBMCC), 9, rue Edward Steichen, 2540 Luxembourg, Luxembourg

Mandy Doering studied chemistry at the University of Saarland, where she received her first degree in 2007. She joined Claus Jacob's group in bioorganic chemistry as part of her undergraduate project and started to work on multifunctional, biologically active redox catalysts. After graduation, Mandy continues to work on the design of multifunctional redox catalysts with regard to potential applications in medicine and agriculture in Claus Jacob's research group.

Mandy Doering, Universität des Saarlandes, School of Pharmacy, Division of Bioorganic Chemistry, 66041 Saarbrücken, Germany

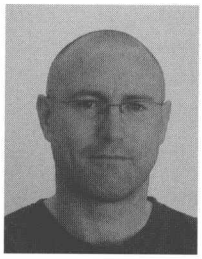
Yuktee Dogra obtained a BSc (Hons) in microbial and cellular biology and a MRes in aquatic ecotoxicology from the University of Plymouth. She is currently in her third year of studying for a PhD in clinical and biomedical science at the Peninsula Medical School. Her project considers the mechanisms and enhancement of photodynamic therapy in the area of dermatology and employs a variety of biological and chemical methodologies. She has two published papers to date on the effects of tritium on the aquatic environment and represents the School's postgraduate students on the research degree committee.

Yuktee Dogra, Cornwall Dermatology Research, Peninsula Medical School, The Knowledge Spa, Truro, Cornwall TR1 3HD, UK



Frederick E. Domann is a professor of radiation oncology in the Free Radical & Radiation Biology Program at The University of Iowa in Iowa City, Iowa, USA. He earned his PhD at the University of Wisconsin-Madison in human cancer biology and subsequently carried out postdoctoral research at The Arizona Cancer Center. He joined the faculty at The University of Iowa in 1993 and has since become an internationally recognized expert in free radical biology and cancer. His research interests include transcriptional regulation and epigenetic control of gene expression in human cancer.

Frederick E. Domann, The University of Iowa, Holden Comprehensive Cancer Center, Carver College of Medicine, Department of Radiation Oncology, Iowa City, IA 52242-1181, USA



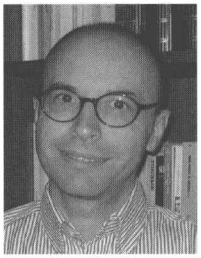
Philip Eaton gained a BSc in biochemistry from Queen Mary College (University of London) in 1989 before completing his PhD studies at the University of Sussex. After postdoctoral work at the Institute of Psychiatry, he joined the Department of Cardiovascular Research, at the Rayne Institute, St. Thomas' Hospital in 1995. He remains at the Rayne Institute and is currently based in the Department of Cardiology. A major focus of his work is the covalent modification of cardiac proteins by oxidants, with a particular emphasis on thiol-targeted events such as *S*-thiolation, interprotein disulfide formation, nitrosylation, sulfenation and sulfination.

Philip Eaton, King's College London, Cardiovascular Division, Department of Cardiology, The Rayne Institute, St. Thomas' Hospital, London SE1 7EH, UK

Paul Eggleton runs the inflammation and autoimmunity group at Peninsula Medical School, University of Exeter, Devon, UK. His interest in the biochemistry of inflammatory pathways developed while studying for his PhD at the Royal College of Surgeons of England in London. His interests in leukocyte biology continued at Boston University Medical School, where he demonstrated that oxidative stress proteins bind to complement proteins and influence innate immunity. His interest in oxidative stress and immunity developed further at Oxford University, where his group focused on the role of complement protein interaction with the oxidative stress protein—calreticulin, and demonstrated that release of

this protein during cell stress modulated autoimmunity and apoptosis. This work is ongoing at Peninsula Medical School.

Paul Eggleton, Universities of Exeter and Plymouth, Peninsula Medical School, St. Luke's Campus, Magdalen Road, Exeter EX1 2LU, UK

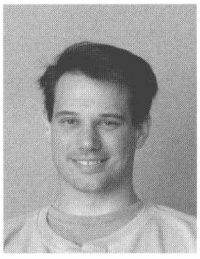


Pietro Ghezzi, PhD, heads the Laboratory of Neuroimmunology at the Mario Negri Institute in Milano. His main research interests are on the role of inflammatory cytokines in diseases of the central nervous system and the redox regulation of immunity with a particular focus on glutathiolation and redox proteomics.

Pietro Ghezzi, Brighton & Sussex Medical School, Trafford Centre, Falmer, Brighton BN1 9RY, UK

Lina Ghibelli gained her laurea cum laude in biology in 1979, folowed by postdoctoral training at the University of Chicago and EMBL in Heidelberg. Since 1991 she has been leading a research group studying the molecular mechanisms regulating the process of cell death by apoptosis.

Lina Ghibelli, Universita' di Roma "Tor Vergata", Dipartimentodi Biologia, via Ricerca Scientifica, 00133 Roma, Italy

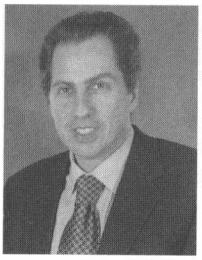


Gregory I. Giles received his PhD from the University of Southampton (UK) and gained postdoctoral experience as a research fellow at the University of Exeter (UK). He was awarded a Frederick Gardner Cottrell Career Enhancement Award to study at the Center for Free Radical Biology at the University of Alabama at Birmingham (USA), followed by his first faculty position as a university research fellow at the University of Sydney (Australia). He was appointed to a lectureship at the University of Otago, Dunedin (New Zealand) in 2008. His research interests include drug design, free radical biology and signal transduction mechanisms.

Gregory I. Giles, Department of Pharmacology, Otago School of Medical Sciences, University of Otago, Dunedin, New Zealand

Geoffrey Gloire is a postdoctoral researcher from the FNRS (Belgian Fund for Scientific Research) at the GIGA-Research Center, Liège, Belgium, in the laboratory of Jacques Piette. He studied biology at the University of Liège and joined the laboratory of Jacques Piette to complete his PhD on the mechanism of NF-κB activation by reactive oxygen species. He now works with his group on the regulation of apoptosis by protein phosphatases and reactive oxygen species in immune cells.

Geoffrey Gloire, University of Liège, Virology-Immunology Unit, GIGA-Research, 1, avenue de l'Hopital, 4000 Liège, Belgium



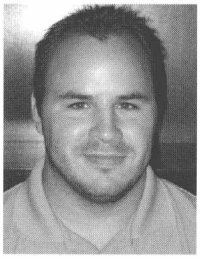
Nicholas J. Gutowski is a consultant neurologist at the Royal Devon and Exeter Foundation Hospital and senior lecturer in the Peninsula Medical School. He has long-standing research interests with publications in several aspects of neuroscience in neurological diseases, including oxidative stress systems, astrocyte and endothelial cell phenotype changes and neuro-oncology as well as interests in neurodevelopment, in particular the congenital cranial dysinnervation disorders.

Janet E. Holley completed a BSc in health science at Exeter University in 1998 and an MSc in advanced neuro- and molecular pharmacology at Bristol University in 1999, where she was involved in a research project investigating the antioxidant status of ventilated premature babies. She has been a member of the research team at the Peninsula Medical School in Exeter since its foundation and has recently completed her PhD. Her primary interests are in the biology and functions of astrocytes and their role in neuropathology, the interactions between astrocytes and endothelial cells, oxidative stress and antioxidant systems in neurological disease, and congenital cranial dysinnervation disorders.

Thomas R. Hurd, Medical Research Council DunnHuman Nutrition Unit, Wellcome Trust/Medical Research Council Building, Hills Road, Cambridge CB2 0XY, UK

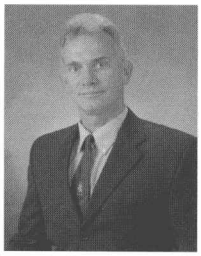
Lars-Oliver Klotz has been an associate professor at the Environmental Health Research Institute at Heinrich-Heine-University in Düsseldorf, Germany, since 2007. He studied biochemistry at the University of Tübingen, and received his PhD in biochemistry from the University of Düsseldorf in 1998. Following postdoctoral studies at the National Institute on Aging in Baltimore, MD, USA, he returned to Düsseldorf in 2000, where he received his lecturing qualification in 2001. Dr. Klotz is a recipient of the Catherine-Pasquier-Award of the European Society of Free Radical Research. His research interests include the biochemistry of oxidative stress, stress-induced signal transduction and molecular processes in aging.

Lars-Oliver Klotz, Department of Molecular Aging Research at Institut für umweltmedizinische Forschung (IUF), 40225 Düsseldorf, Germany



David M. Krzywanski received his PhD in environmental health science in 2006 from the University of Alabama, Birmingham, USA. His research centers on free radical biology and human health and disease, with his interests ranging from the enzymatic regulation of glutathione synthesis to the effect of environmental nitrogen dioxide on acute epithelial cell injury. Currently, Dr Krzywanski is a postdoctoral fellow in the UAB Department of Pathology, working under Dr S. Ballinger on projects aimed at understanding the role of mitochondrial signaling in the development of cardiovascular disease.

David M. Krzywanski, University of Alabama at Birmingham, Department of Center for Free Radical Biology, Birmingham, AL, USA



Christiaan Leeuwenburgh received his PhD from the University of Illinois, Urbana-Champagne in 1995. He completed his postdoc in internal medicine at the Division of Geriatrics and Gerontology and Division of Atherosclerosis, Nutrition and Lipid Research at Washington University School of Medicine, Saint Louis. He became an assistant professor at the University of Florida in 1998, where he is currently a professor within the Department of Aging and Geriatric Research, College of Medicine and Institute on Aging, as well as heading the Division of Biology of Aging. Dr Leeuwenburgh's major research focus is on understanding the molecular mechanism of oxidative stress and apoptosis with age in rodent models.

Christiaan Leeuwenburgh, University of Florida, College of Medicine, Division of Biology of Aging, Department of Aging and Geriatrics, Institute on Aging, Biochemistry of Aging Laboratory, Gainesville, FL 32610-0107, USA

Kirsty Line graduated in biochemistry from the University of Wales, Aberystwyth, in 2000. She was awarded her PhD in 2004 in the group of Professor Jenny Littlechild, University of Exeter, investigating novel gamma-lactamase enzymes important in industrial biotransformation reactions, in conjunction with Chirotech Technology Ltd, Cambridge. She has continued to work with Professor Littlechild, carrying out studies on human antioxidant enzymes peroxiredoxin and sulfiredoxin.

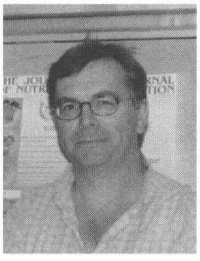
Kirsty Line, Universities of Exeter and Plymouth, Peninsula Medical School, St Luke's Campus, Magdalen Road, Exeter EX1 2LU, UK

Jennifer A. Littlechild carried out her PhD in biophysics at Kings College, London University, UK, followed by a postdoc fellowship at the Biochemistry Department of Princeton University, USA. In 1975 she became a group leader at the Max-Planck Institute for Molecular Genetics in Berlin, Germany, returning to the UK in 1980 to Bristol University. She is currently professor of biological chemistry and director of the Exeter Biocatalysis Centre, School of Biosciences. She has over 110 refereed publications to her name and has presented her research work internationally. Her current research involves the structural and mechanistic characterization of human enzymes involved in oxidative stress, aggregation of β-amyloid protein in Alzheimer's disease, GSTs and response to anticancer drugs and mutations in key enzymes resulting in diabetes and fructose intolerance.

Jennifer A. Littlechild's, Universities of Exeter and Plymouth, PeninsulaMedical School, St. Luke's Campus, Magdalen Road, Exeter EX1 2LU, UK

Philip K. Moore received his BSc and PhD from the University of London. In recent years he was head of the Department of Pharmacology at the National University of Singapore and is now professor of integrative pharmacology at King's College in London. He has been researching biologically active gases for the last 30 years and in that time has reported the characterization of several inhibitors of nitric oxide synthase and latterly hydrogen sulfide donor drugs. His major research interests are in the local regulation of blood flow and permeability, inflammatory mechanisms in arthritis and shock and in the regulation of local mediator biosynthesis and activity.

Philip K. Moore, King's College London, Pharmaceutical Science Division, Franklin-Wilkins Building, 150 Stamford Street, London SE1 9NH, UK

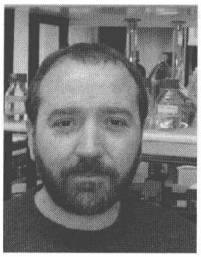


Michael P. Murphy received his BA in chemistry from Trinity College, Dublin in 1984 and his PhD in biochemistry from Cambridge University in 1987. After spells in the USA, Zimbabwe and Ireland, he took up a position in the Biochemistry Department for the University of Otago, Dunedin, New Zealand in 1992. In 2001 he moved to the MRC Dunn Human Nutrition in Cambridge, UK, where he is a group leader. Currently his special interests are in targeting small molecules such as antioxidants to mitochondria, and in understanding how modifications to the thiol status of mitochondrial proteins contributes to oxidative damage and redox signaling.

Michael P. Murphy, Medical Research Council Dunn Human Nutrition Unit, Wellcome Trust/Medical Research Council Building, Hills Road, Cambridge CB2 0XY, UK

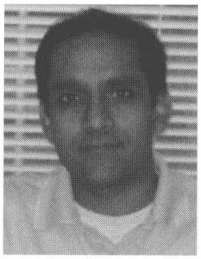
Following a BSc in human nutrition and dietitics at the University of Dublin, **Valerie O'Donnell** gained her PhD in biochemistry from the University of Bristol, in the field of neutrophil NADPH oxidase. This led to two postdoc positions, first at the University of Bern, Switzerland, and then the University of Alabama at Birmingham, USA. In Switzerland, she worked on mechanisms of TNF cytotoxicity and free radical generation in fibroblasts. At UAB, she worked with Bruce Freeman on interactions of nitric oxide with oxidizing lipids. Following this, she returned to the UK on a Wellcome Trust RCD Fellowship at Cardiff University. She is currently a group leader, working in the area of free radical and lipid biochemistry, related to vascular inflammation.

Valerie B. O'Donnell, Cardiff University, School of Medicine, Department of Medical Biochemistry and Immunology, Heath Park, Cardiff CF14 4XN, UK



Reinald Pamplona is professor of physiology at the Medical School of the University of Lleida, Spain. He received his MD in 1987 from the University of Barcelona and continued his research under Professor Gustavo Barja, at the Complutense University of Madrid (Spain), and Professor John W. Baynes, at the University of South Carolina (USA), concerning the detection and measurement of mitochondrial free radical production, antioxidant activities, and oxidative-derived molecular damage. Following this, he received his PhD in 1993 from the University of Barcelona, and has since followed the role of oxidative stress in aging and life span and age-related diseases. Currently, he is the head of the Department of Experimental Medicine and director of the Metabolic Physiopathology Research Group at the Biomedical Research Institute of Lleida (Spain).

Reinald Pamplona, University of Lleida-IRBLLEIDA, Faculty of Medicine, Departament of Experimental Medicine, Lleida 25008, Spain



Dr Rakesh P. Patel gained his PhD from the University of Essex, UK, in 1996 under Professor M.T. Wilson. In 1997 he joined Dr Victor Darley-Usmar's laboratory as a postdoc scientist in the Department of Pathology, University of Alabama at Birmingham, where he is currently associate professor in the Department of Pathology and co-director of the Department of Pathology Graduate Program. Dr Patel is involved in numerous research projects focused on mechanisms by which inflammation causes injury and on developing novel therapeutic modalities.

Rakesh P. Patel, University of Alabama at Birmingham, Department of Pathology, 901 19th Street South, BMR-2, Room 302, Birmingham, AL 35294, USA