Oxidative Stress in Applied Basic Research and Clinical Practice

Editor-in-Chief
Donald Armstrong

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Note from the Editor-in-Chief

All books in this series illustrate point-of-care testing and critically evaluate the potential of antioxidant supplementation in various medical disorders associated with oxidative stress. Future volumes will be updated as warranted by emerging new technology, or from studies reporting clinical trials.

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Preface

Oxidative stress is a product balance between pro-oxidants and antioxidants. Reactive oxygen species are normally generated by cells and a certain level of oxidative stress plays an important role as second messenger under physiological conditions. However when oxidative stress is increased, whether due to blunted antioxidant defenses or increased generation of reactive oxygen species, it can have a deleterious effect on almost any organ/system in the human. Increased oxidative stress has been shown to promote vasoconstriction, vascular remodeling, inflammation, and fibrosis in different organs. Specifically, as a result of the "oxidative stress modification hypothesis" increased oxidative stress has been directly related to the development of atherosclerosis and vascular disease. Abundant evidence mainly from experimental studies supported a pathophysiological role of increased oxidative stress on the development and progression of vascular disease, which have served as the impetus for many clinical studies to assess the impact of reestablishing oxidant balance in different vascular disease conditions. However, most of them have not provided conclusive or consistent results. Therefore, the relevance of oxidative stress as therapeutic target has been put into question as its pathophysiological role revised.

Many areas of research beyond oxidative stress have had trouble in translating preclinical studies to clinical studies. It is important to make sure that studies, both preclinical and clinical, have the intended hypothesis and are properly designed. Only then, accurate conclusions could be drawn. The goal of this book is to describe a roadmap of the knowledge in the area of oxidative stress and the development of vascular disease and to put in perspective where the scientific field is regarding the translation of preclinical knowledge to clinical trials.

In the first chapters of this book, we will examine the role of oxidative stress under physiological conditions. Subsequent chapters will address the relationship between oxidative stress and the development of vascular disease, and identify and discuss the background that led to clinical trials. The last part of the book will be dedicated to the clinical data that is currently available regarding interventions or

attempts to preserve oxidant stress under different conditions. The intention of this last section is to put into perspective the previous clinical studies, what answers they attempted to answer and why they may/may not have tested the intended hypothesis.

It is the hope of the Editors that this book will inspire scientists of many backgrounds to be involved in the field of oxidative stress and vascular disease.

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About the Authors

Akshaar Brahmbhatt is currently completing his M.D. at Rutgers University—New Jersey Medical School. His research focuses on the roles of hypoxia, inflammation, oxidative stress, and angiogenesis in the setting of vascular pathologies.

Alastair M. Buchan Professor Buchan is Head of the Medical Sciences Division, Dean of Medicine, Fellow of Corpus Christi College, and Professor of Stroke Medicine at the University of Oxford. He trained at Cambridge, Oxford, and Cornell before moving to Calgary, where he became Director of the Stroke Program. He returned to Oxford in 2005 to establish the thrombolysis service at the John Radcliffe Hospital. His research interests include the role of hamartin in endogenous neuroprotection and pericyte function in models of stroke. Professor Buchan is a Fellow of the Academy of Medical Sciences and an Honorary Member of the American Neurological Association, among other professional accolades.

Sophocles Chrissobolis, Ph.D. is currently an Assistant Professor of Pharmacology in the Department of Pharmaceutical and Biomedical Sciences in the College of Pharmacy at Ohio Northern University (ONU). At ONU, his research is focused on mechanisms that promote hypertension and vascular dysfunction in experimental models of hypertension. His Ph.D. studies at the University of Melbourne focused on mechanisms regulating cerebral vascular function in health and disease. His postdoctoral studies at the University of Iowa, USA, and Monash University, Australia, were supported by fellowships and focused on mechanisms promoting, and protecting against, oxidative stress, vascular dysfunction, and inflammation in experimental hypertension.

Quynh N. Dinh is currently completing her PhD at Monash University. Her research focuses on the roles of aging, inflammation, oxidative stress, and vascular

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Grant R. Drummond, Ph.D. is a Senior Research Fellow of the National Health and Medical Research Council of Australia and co-leader (with Professor Chris Sobey) of the Vascular Biology and Immunopharmacology Group in the Cardiovascular Disease Program, Biomedicine Discovery Institute, and Department of Pharmacology, Monash University, Australia. His research interests are on the roles of oxidative and immune mechanisms in the pathophysiology of hypertension, atherosclerosis, and stroke. Grant Drummond received his Ph.D. from the Department of Pharmacology, University of Melbourne, in 1998. He moved to Monash University in 2004 after completing postdoctoral training at Emory University (Atlanta, USA) under Professor David Harrison, and at the Howard Florey Institute (Melbourne, Australia) under Professor Greg Dusting.

Frank M. Faraci received a Ph.D. in Physiology from Kansas State University. He is currently Professor of Internal Medicine and Pharmacology at the University of Iowa. His laboratory focuses on defining molecular mechanisms that underlie large and small vessel disease in brain, with an emphasis on the impact of risk factors for vascular disease—particularly hypertension and aging. He has published over 280 journal articles, served as Associate Editor for *Stroke* and *Arteriosclerosis, Thrombosis, and Vascular Biology (ATVB)* and is currently on the editorial board of the *American Journal of Physiology, Circulation Research*, *Journal of Cerebral Blood Flow and Metabolism, ATVB*, and the *Journal of Neuroscience*. Dr. Faraci's laboratory is funded by the National Institutes of Health, the Department of Veterans Affairs, and the Fondation Leducq.

Gina Hadley Dr. Hadley is an academic clinician with an interest in geriatrics and stroke at the point of submitting her PhD "Mechanisms underlying the endogenous neuroprotection of hamartin in ischaemic stroke" with Professor Alastair Buchan. She has a B.Sc. (Hons.) in Pharmacology with Industrial Experience, spending a year at Queen's University, Canada. She studied Graduate Entry Medicine at the University of Oxford, completing a Wellcome-funded elective project at the Kenya Medical Research Institute (KEMRI). Dr. Hadley is a Tutor in Clinical Medicine at Harris Manchester College, Oxford. She has recently completed a Masters in Evidence Based Medicine and has membership of the Royal College of Physicians.

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Lilach O. Lerman, M.D., Ph.D. is currently a Professor of Physiology and Medicine and the Director of the Hypertension research at Mayo Clinic. Dr. Lerman obtained her medical degree at the Technion University in Israel and her PhD in Physiology & Biomedical Engineering at Mayo Clinic. Her research is focused on understanding the pathophysiology of hypertension and atherosclerosis, using state-of-the-art imaging modalities. Over the years, she also has had special interest in the role of oxidative stress in kidney disease. More recently, she has integrated her expertise in the study of pathophysiology with the development of novel therapeutics, like cell therapy and others.

Joy Lincoln, Ph.D. is a Principal Investigator at Nationwide Children's Hospital and Associate Professor of Pediatrics at The Ohio State University. Her research program is focused on defining the mechanisms underlying the onset and progression of congenital and acquired heart valve disease. This interest stems from her postdoctoral training under the mentorship of Dr. Katherine Yutzey at Cincinnati Children's Hospital Medical Center. Dr. Lincoln obtained her undergraduate degree in Biomedical Sciences from Durham University in the United Kingdom and graduated with a Ph.D. in Molecular and Developmental Biology from the same institution.

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Ain A. Neuhaus obtained his B.A. in Medical Sciences from Somerville College, University of Oxford (1st Class, 2012). He subsequently started a D.Phil. in Medical Sciences with Prof. Alastair Buchan at the Radcliffe Department of Medicine in Oxford, using in vivo and in vitro models of stroke to investigate pericyte contractility and regulation of cerebral blood flow following ischemia and reperfusion, and is now in his final year of D.Phil. studies.

T. Michael De Silva received a PhD in Pharmacology from Monash University in Melbourne, Australia. He completed his postdoctoral training with Dr. Frank M. Faraci at the University of Iowa. Following his postdoctoral training, Dr. De Silva returned to Monash University to establish his own research program. He is the recipient of a National Health and Medical Research Council of Australia Early Career Fellowship. Dr. De Silva's research aims to understand mechanisms that regulate cerebral microvascular function and the impact that microvascular dysfunction has on cognition. Dr. De Silva is an emerging young investigator in the field of cerebrovascular disease and has published 14 journal articles to date.

Chris Sobey, Ph.D. Professor Chris Sobey's research has focused on vascular diseases involving oxidative stress and inflammation, especially in the brain and cerebral circulation. He obtained his Ph.D. at the University of Melbourne for his studies of coronary vascular function following myocardial ischemia. He then completed a postdoctoral Fellowship at the University of Iowa where he gained expertise in the study of cerebral artery function in vivo, and returned to Australia where he is an NHMRC Senior Research Fellow with an established research program in experimental cerebrovascular disease and stroke. His research is now investigating the inflammatory mechanisms occurring in the brain after stroke in order to identify and develop novel approaches to ultimately treat stroke patients.

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About the Editors

Alejandro R. Chade, M.D., F.A.H.A. is a clinically trained Cardiologist who joined the Mayo Clinic following completion of his clinical training for postdoctoral research training in renovascular hypertension and chronic renal disease. Dr. Chade is currently a Tenured Professor in the Department of Physiology and Biophysics at the University of Mississippi Medical Center. His research focuses on the mechanisms of renal injury and therapeutic developments for chronic renovascular disease with a major focus on the renal microcirculation. His research is highly translational and has been published in 70 peer-reviewed papers, book chapters, and is consistently presented in national and international meetings. Dr. Chade is an active member of the American Heart Association, American Physiological Society, American Society of Nephrology, and the European Renal Association.

Jordan D. Miller, Ph.D. is an Associate Professor of Surgery who joined Mayo Clinic in 2009. He received his Ph.D. in Exercise Physiology from the University of Wisconsin-Madison in 2005 and pursued postdoctoral training with Dr. Donald Heistad at the University of Iowa. Dr. Miller's program focuses on mechanisms that contribute to the pathogenesis of age-related cardiovascular diseases, including calcific aortic valve stenosis, atherosclerosis, and stiffening of conduit arteries. His program also aims to bridge the gap from bench to bedside and recently initiated Phase I and II clinical trials aimed at testing the therapeutic efficacy of re-activation of nitric oxide signaling in patients with aortic valve stenosis. He is very active in the American Heart Association and has held several leadership positions in the ATVB Council, is a member of the American Physiological Society, serves on the Board of Directors for the Heart Valve Society, and serves on the Editorial Boards of *Circulation Research*, *American Journal of Physiology-Heart and Circulatory Physiology*, and *the Journal of Heart Valve Disease*.

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