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Redox Pioneer: Professor Roland Stocker

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Professor Roland Stocker

Abstract

Dr. Roland Stocker (Ph.D. 1985) is recognized here as a Redox Pioneer, because he has published one article on antioxidant/redox biology as first author that has been cited over 1000 times and has published another 32 articles, each cited over 100 times. Dr. Stocker received his undergraduate education at the Federal Institute of Technology Zürich, Switzerland (1975–1981), followed by postgraduate training at the Australian National University Canberra, Australia (1982–1985) and postdoctoral training at the University of California, Berkeley (1986–1987), and the University of Berne, Switzerland (1987–1988). Dr. Stocker's top scientific contributions are in the following areas: (i) molecular action and interaction of nonproteinaceous antioxidants, particularly bilirubin, α-tocopherol, and ubiquinol-10; (ii) lipoprotein lipid oxidation and its inhibition, with a particular focus on how α-tocopherol affects these processes; (iii) the role of arterial lipoprotein lipid oxidation in atherosclerosis and related diseases; (iv) modes of antiatherosclerotic action of probucol and the involvement of heme oxygenase-1 in vascular protection; and (v) the regulation of indoleamine 2,3-dioxygenase and its contribution to vascular tone and blood pressure in inflammatory diseases. *Antioxid. Redox Signal.* 15, 3101–3105.

Critical thinking, hard work and tenacity and trust in one's own convictions are the cornerstones of success.
—Prof. Roland Stocker

Background, Development, and Training

ROLAND STOCKER COMPLETED his undergraduate degree at the Federal Institute of Technology in Zürich Switzerland in 1981 and his Ph.D. studies at the Australian National University in Canberra in 1985. I was fortunate enough to be an Associate Supervisor of his Ph.D. work and it was obvious from the beginning that he was a rare talent. His primary supervisor was Dr. Maurie Weidemann, a talented and energetic metabolic biochemist who had studied under Krebs. Roland's doctoral work focused on the role of redox processes in malaria.

Roland then undertook a fairly brief but enormously productive period of postdoctoral research in Bruce Ames' laboratory at the University of California, Berkeley (1986–1987). Two of his "Citation Classics" (6, 9) originate from this period. He then briefly returned to Switzerland as Assistant Professor at the University of Berne (1987–1988), where he worked with Ernst Peterhans. This was followed by a permanent move to Australia in 1988, since when he has led research teams at

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Author note: Nicholas Hunt has known Professor Stocker since 1982, when he was an associate supervisor of the professor's Ph.D. studies at the Australian National University, Canberra. Since Professor Stocker's permanent return to Australia in 1988 the author has collaborated with him on a number of research projects and worked with him within the Society for Free Radical Research (Australasia).

For a list of frequently cited articles published by Prof. Stocker, see Supplementary Tables S1 and S2, available online at www.liebertonline.com/ars.

Sydney's Heart Research Institute (1988–2001), the University of New South Wales (2002–2006), and the University of Sydney (2007 to present), where he is currently Chair of Biochemistry in Vascular Medicine at the Bosch Institute and the Center for Vascular Research.

Area of Interest in Redox Biology

It was the work on cytochrome P-450 and the intellectual atmosphere in the laboratory of Christoph Richter at the Federal Institute of Technology in Zurich that sparked the fascination of Roland Stocker with reactive oxygen species. His early interest in the respiratory burst of neutrophils was followed by the investigation of oxidative stress as part of the innate immune response to malaria during his Ph.D. studies. However, it was the jaundice developed by his elder daughter Sophie-Lena after her birth in 1983 that sparked the interest of Dr. Stocker in the oxidative pathway of heme degradation leading to the formation of bilirubin. This interest came to fruition during his postdoctoral studies in the Bruce Ames laboratory and the collaborations with Yorihiro Yamamoto, Antony MacDonagh, and Alexander Glazer. From the discovery of bilirubin as an antioxidant developed his long-term interests in low-molecular weight antioxidants and how they protect against oxidative damage in disease pathogenesis.

In the early stage of his career, the thinking of how nonproteinaceous antioxidants work was largely limited to the interception of oxidants by each antioxidant in isolation. From this developed the concept of antioxidant networks, in which different antioxidants interact with each other, and "first-line" antioxidants were distinguished (6). It was a time when chemical methods and principles were applied to *in vitro* systems by influential redox chemists, including Keith Ingold and Etsuo Niki. As knowledge increased, so did realization of the complex nature of antioxidant networks in biological systems. This initially included physical (*e.g.*, compartments) and temporal separation of redox reactions and the increasing realization that some low-molecular-weight "antioxidants" provided protection indirectly *via* induction of (antioxidant) defense enzymes and pathways. Indeed, one of Roland's current interests is how the various antioxidant networks, composed of nonproteinaceous and proteinaceous components, interact with each other in complex biological systems.

Description of Key Finding 1

The discovery of bilirubin as an antioxidant

His 1987 *Science* paper on the possible physiological importance of bilirubin as a physiological chain-breaking antioxidant (9) is Dr. Stocker's most cited paper. By demonstrating that bilirubin is an antioxidant, the work changed the view that heme degradation to bile pigments by heme oxygenase (HO) simply reflects a catabolic pathway that generates waste products. This finding, now acknowledged in textbooks, led to the paradigm that "conversion" of the pro-oxidant heme to antioxidant bile pigments by the action of HO-1 provides biological benefits. In a recent publication (4), Dr. Stocker extends the proposed benefits of heme metabolism to gene transcription regulatory activity of HO-1 (Fig. 1).

Dr. Stocker's discovery of this novel biological role for bilirubin provided the early rationale for pursuing the translational applications of the products of HO-1 enzymatic action, that is, biliverdin/bilirubin and carbon monoxide. Indeed, inhaled carbon monoxide is currently in clinical trials as a therapeutic in chronic pulmonary obstructive disease and renal transplantation. Further, pharmacological application of biliverdin/bilirubin is under consideration as a therapy in vascular injury and transplantation. The work of Dr. Stocker on the beneficial activities of bilirubin has also contributed to a change in clinical practice in neonatal intensive care units (NICU) when babies suffer from hyperbilirubinemia and when therapy against it is introduced.

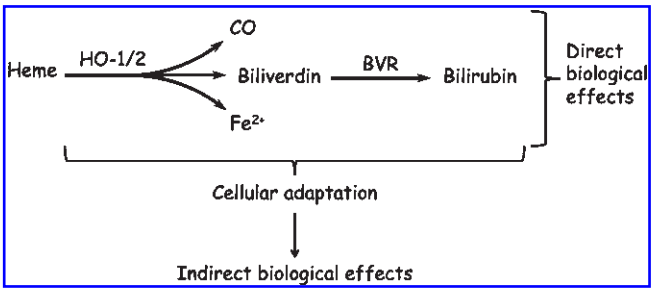

FIG. 1. Concept of heme catabolism by HO-1 affording biological effects directly *via* its enzymatic activity, including the formation of the bile pigment biliverdin (converted to bilirubin by BVR), and indirectly *via* cellular adaptation mediated by transcriptional regulation, as recently described by Collinson *et al.* (4). BVR, biliverdin reductase; HO, heme oxygenase.

In recent years, Dr. Stocker's research on HO-1 has shown for the first time that a class of antioxidants represented by probucol protect against atherosclerosis and related diseases indirectly *via* induction of HO-1 in vessel wall cells (15) rather than by inhibiting the oxidative modification of low-density lipoprotein (2). This represents a significant change in thinking about how low-molecular-weight antioxidants protect against disease and this principle may be more generally applicable than appreciated at present. The finding has also provided further evidence that induction of HO-1 represents a novel drug target for cardiovascular disease (12).

Description of Key Finding 2

Molecular action of vitamin E

Dr. Stocker's seminal work on the molecular action of α-tocopherol in lipoproteins explains how vitamin E overall only retards (rather than inhibits) lipoprotein lipid oxidation, and how the vitamin becomes a pro-oxidant *via* tocopherol-mediated peroxidation (TMP). The concept of TMP, developed by Dr. Stocker in collaboration with Vincent Bowry and Keith Ingold, is described in a series of publications including a seminal paper in *Journal of American Chemical Society* (1) that has been cited over 460 times to date. The TMP model is based on physical–chemical principles established in emulsion polymerization, and it establishes how substantial lipid oxidation could occur in human blood or arteries despite the presence of normal amounts of vitamin E (Fig. 2).

Initially this idea provoked a furious debate in the scientific community, which has now abated. The TMP model shifts the paradigm that vitamin E always acts as a chain-breaking antioxidant and provides a conceptual basis for "co-antioxidants"

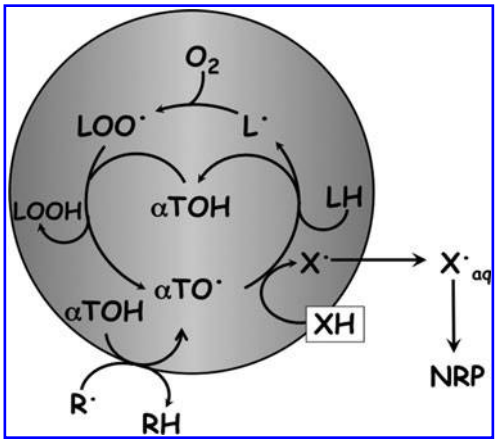

FIG. 2. Concept of tocopherol-mediated peroxidation and its inhibition by coantioxidants (XH), as described by Bowry and Stocker (1).

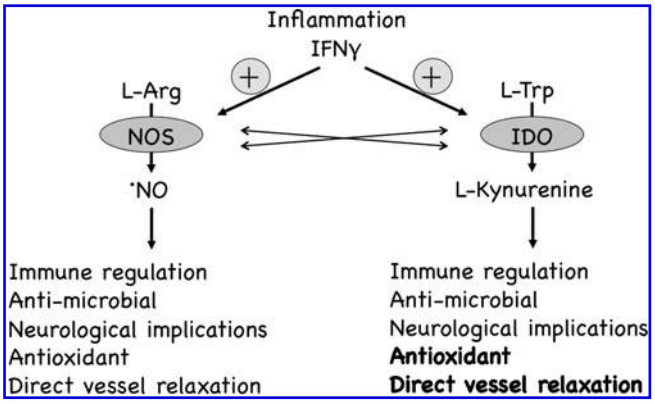

FIG. 3. Similarities between events triggered by NOS and IDO. The roles of IDO-derived products in antioxidation and vessel relaxation (shown in bold) were reported by Christen *et al.* (3) and Wang *et al.* (13), respectively. IDO, indoleamine 2,3-dioxygenase-1; NOS, nitric oxide synthase.

that act by preventing the pro-oxidant activity of vitamin E. A translational outcome of this work is the change in clinical practice concerning the use of vitamin E-rich parenteral nutrition in NICU.

Dr. Stocker later provided landmark evidence (14) that despite coantioxidants effectively inhibiting lipoprotein lipid oxidation in the arterial wall, atherogenesis was not always affected. These findings supported the *in vivo* relevance of the TMP model of lipoprotein oxidation and demonstrated the dissociation of arterial lipoprotein oxidation from the process of atherosclerosis. The latter discovery has fundamentally challenged the "Oxidative Modification Hypothesis" of atherosclerosis, according to which lipoprotein lipid oxidation in the arterial wall is an early event and causes atherosclerosis. Dr. Stocker, with Dr. John Keaney Jr., wrote a definitive review on the role of oxidative processes in atherosclerosis in which they provided an alternative theory of atherosclerosis that reconciles the above controversies and other literature findings (11).

Description of Key Finding 3

IDO and vascular tone

Dr. Stocker has a long-standing interest in the tryptophan-metabolizing enzyme indoleamine 2,3-dioxygenase-1 (IDO-1). He was the first to point out the antioxidant activities of some of the tryptophan metabolites formed along the kynurenine pathway (3), and his laboratory recently added to the discussion of whether superoxide anion is required as a cofactor for cellular IDO-1 activity (8). More recently, Dr. Stocker led a multi-institutional team that demonstrated the identification of tryptophan metabolism to kynurenine as a novel pathway contributing to endothelium-dependent relaxation and decreased blood pressure in inflammation (13), thereby further extending the functional similarities between IDO and nitric oxide (NO) synthase (Fig. 3).

An important aspect of this latest discovery is its potential to compensate for loss of biological activity of NO in inflammatory conditions that are associated with oxidative stress and the potential oxidation of soluble guanylate cyclase so that the enzyme becomes heme free and, hence, refractory to activation by NO. This discovery seems likely to open up a new field of IDO-1 research and may provide the basis of novel therapeutic target(s) and methods of treating abnormal blood pressure conditions.

Other Achievements

Dr. Stocker's work on low-molecular-weight antioxidants includes the demonstration of the powerful protective properties of ascorbic acid and reduced coenzyme Q_{10} in human blood plasma and lipoproteins. In collaboration with Balz Frei and Bruce Ames, the work on vitamin C (6) introduced the concept of "first-line" antioxidant defense and also showed for the first time that substantial lipid oxidation can occur in human blood despite the presence of normal amounts of α-tocopherol. Dr. Stocker's research on the antioxidant activities of coenzyme Q_{10} in lipoproteins (10) extended the biological functions of this molecule from its role in mitochondrial respiration to a new field.

Dr. Stocker is actively involved in the Q_{10} research community and is a founding member of the International Coenzyme Q_{10} Association, acting as chair of the scientific committee for 10 years. He was commissioned by the National Institutes of Health to author a definitive review on coenzyme Q_{10} for the *Encyclopedia of Dietary Supplements* (5), which was recently updated. Similarly, Roland was commissioned by the National Heart Foundation of Australia to write a position statement on the "Use of antioxidant supplements in coronary heart disease" (7). This position statement has since been adopted and reinforced and recently extended to a national position on "Antioxidants in food, drinks and supplements for cardiovascular health."

Roland Stocker has served on the editorial boards of all journals focusing on redox processes in biology. He is a past president of the Society for Free Radical Research (SFRR) Australasia, was the secretary of the Organizing Committee of the 1994 Conference of the SFRR International, and initiated the biennial joint scientific meetings of SFRR Australasia and SFRR Japan. He led a successful bid for the Eighth International Heme Oxygenases Conference to be held in Sydney in 2013.

Dr. Stocker's review on the role of oxidative modifications in atherosclerosis (11) was identified by Thomson ISI® in 2006 as one of the most cited recent papers in the field of biology and biochemistry, with over 600 citations to date. In 1996, Roland was the inaugural recipient of the Simon Wolff Contrarian Award from the journal *Redox Report*. This award, for those "who upset established scientific 'apple carts,'" recognized his work on vitamin E's ability to enhance the oxidation of low-density lipoprotein. In 2007 he received the honor of being the Paul Nestel Lecturer of the Australian Atherosclerosis Society in recognition of his outstanding contribution to atherosclerosis research in Australia. In 2010 Dr. Stocker was honored with a Lifetime Achievement Award of the SFRR Australasia in recognition of his contribution to the research community and excellence in research.

Current Position

Roland Stocker is currently the Chair of Biochemistry in Vascular Medicine and head of the University of Sydney node of the Center for Vascular Research. He is a fellow of the National Health and Medical Research Council of Australia since 1994, and a Senior Principal Research Fellow since 2001. In 2010 Roland established the Bosch Institute's Oxidative Stress Bioanalytical Facility to develop and apply state-of-the-art measurement of oxidative stress in cells for local and national researchers.

Those who know Roland Stocker will acknowledge that he has enormous intellectual stamina and the courage to defend his ideas, regardless of whether they are fashionable. Some of his strength of character and conviction may have been forged in the highly testing environment of competitive rowing—Roland and his identical twin brother, Peter, rowed in the Swiss four at the Moscow Olympics. Indeed, a common saying of Roland is "critical thinking, hard work and tenacity and trust in one's own convictions are the cornerstones of success." Roland is a familiar person in parts of Sydney, hurtling along on his bicycle or swimming in the sea or the local pool. He is a good family man and a loyal friend to many. I am privileged to have known him and worked with him.

Acknowledgments

Professor Roland Stocker thanks the various governmental, institutional, private, and commercial sources that have supported his research continuously over the years, particularly the National Health and Medical Research Council of Australia. Professor Stocker was privileged to work with, and wishes to acknowledge, the contributions of many gifted and hardworking students, postdoctoral scientists, fellows, colleagues, and coauthors. Special thanks goes to the following key people who have helped especially in Professor Stocker's life and career development: his former rowing coach, Stephan Fröhlich, for instilling tenacity and for his wisdom on how to plan and successfully pursue goals; Dr. Christoph Richter, for his early advice that "in science, trust is good but control is better"; Dr. Nicholas Hunt, for his mentorship and friendship for nearly 30 years and for his continued reminder that "details matter"; Dr. Bruce Ames, for being a leading example of enthusiasm and excitement, for thinking outside the box, and for instilling the belief that one can make major discoveries in science; and Dr. Roger Dean, for unreservedly providing a great opportunity to become an independent investigator. Finally, Professor Stocker thanks his two daughters Sophie-Lena and Verena for the enormous enrichment of his life and, most importantly, his wife Dr. Maree Stenglin for her unwavering support, unlimited love, and belief in him.

References

1. Bowry VW and Stocker R. Tocopherol-mediated peroxidation. The pro-oxidant effect of vitamin E on the radical-initiated oxidation of human low-density lipoprotein. *J Am Chem Soc* 115: 6029–6044, 1993.
2. Choy K, Beck K, Png FY, Wu BJ, Leichtweis SB, Thomas SR, Hou JY, Croft KD, Mori TA, and Stocker R. Processes involved in the site-specific effect of probucol on atherosclerosis in apolipoprotein E gene knockout mice. *Arterioscl Thromb Vasc Biol* 25: 1684–1690, 2005.
3. Christen S, Peterhans E, and Stocker R. Antioxidant activities of some tryptophan metabolites: possible implication for inflammatory diseases. *Proc Natl Acad Sci USA* 87: 2506–2510, 1990.
4. Collinson EJ, Wimmer-Kleikamp S, Gerega SK, Yang YH, Parish CR, Dawes IW, and Stocker R. The yeast homolog of heme oxygenase-1 affords cellular antioxidant protection via the transcriptional regulation of known antioxidant genes. *J Biol Chem* 286: 2205–2214, 2011.
5. Dallner G and Stocker R. Coenzyme Q_{10}. In: *Encyclopedia of Dietary Supplements*, edited by Coates P, Blackman MR, Cragg G, Levine M, Moss J, and White P. New York: Marcel Dekker, 2005, pp. 121–131.
6. Frei B, Stocker R, and Ames BN. Antioxidant defenses and lipid peroxidation in human blood plasma. *Proc Natl Acad Sci USA* 85: 9748–9752, 1988.
7. Kritharides L and Stocker R. The use of antioxidant supplements in coronary heart disease. *Atherosclerosis* 164: 211–219, 2002.
8. Maghzal GJ, Thomas SR, Hunt NH, and Stocker R. Cytochrome b_5, not superoxide anion radical, is a major reductant of indoleamine 2,3-dioxygenase in human cells. *J Biol Chem* 283: 12014–12025, 2008.
9. Stocker R, Yamamoto Y, McDonagh AF, Glazer AN, and Ames BN. Bilirubin is an antioxidant of possible physiological importance. *Science* 235: 1043–1046, 1987.
10. Stocker R, Bowry VW, and Frei B. Ubiquinol-10 protects human low density lipoprotein more efficiently against lipid peroxidation than does a-tocopherol. *Proc Natl Acad Sci USA* 88: 1646–1650, 1991.
11. Stocker R and Keaney JF, Jr. Role of oxidative modifications in atherosclerosis. *Physiol Rev* 84: 1381–1478, 2004.
12. Stocker R and Perrella MA. Heme oxygenase-1. A novel drug target for atherosclerotic diseases? *Circulation* 114: 2178–2189, 2006.
13. Wang Y, Liu H, McKenzie G, Witting PK, Stasch JP, Hahn M, Changsirivathanathamrong D, Wu BJ, Ball HJ, Thomas SR, and Others. Kynurenine is an endothelium-derived relaxing factor produced during inflammation. *Nat Med* 16: 279–285, 2010.
14. Witting PK, Pettersson K, Östlund-Lindqvist A-M, Westerlund C, Wågberg M, and Stocker R. Dissociation of atherogenesis from aortic accumulation of lipid hydro(pero)xides in Watanabe heritable hyperlipidemic rabbits. *J Clin Invest* 104: 213–220, 1999.
15. Wu BJ, Kathir K, Witting PK, Beck K, Choy K, Li C, Croft KD, Mori TA, Tanous D, Adams MR, and Others. Antioxidants protect from atherosclerosis by a heme oxygenase-1

pathway that is independent of free radical scavenging. *J Exp Med* 203: 1117–1127, 2006.

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Abbreviations Used

BVR = biliverdin reductase
HO = heme oxygenase
IDO = indoleamine 2,3-dioxygenase-1
NO = nitric oxide
NOS = nitric oxide synthase
TMP = tocopherol-mediated peroxidation