Chapter 1
Introduction

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Nature provides a treasure chest which is filled with a huge range of diverse and exciting natural products. Among them, we can find a wide variety of primary and secondary metabolites which originate from plants, fungi, bacteria, and animals and for us possess interesting practical uses in the context of nutrition, medicine, and agriculture. In between the many and extraordinarily diverse natural compounds, redox active secondary metabolites stand out for a number of reasons and, not surprisingly, have recently attracted considerable interest in research and development. These compounds have also been at the center of the European Marie Curie Initial Training Network "RedCat" whose activities are reflected throughout this book (see Explanatory Box 1).

Explanatory Box 1: The "RedCat" Initial Training Network

As part of Framework 7, the European Commission has provided substantial funding to promote the training of Early Stage and Experienced Researchers (ESR, ER, respectively) under the Marie Curie Action. The training network

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"RedCat" has been one of those international, multisite networks, which in 2008–2012 has provided training for ten ESR and four ER at ten partner institutions (and eight associated partners) across Europe. "RedCat" has been coordinated by Claus Jacob, who is also one of the editors of this book. The acronym actually stands for 'redox catalysts', and in many ways finds its reflection in the topics covered by this book. Indeed, all editors of the book and most of the contributors were involved heavily in "RedCat" training and research activities, either as partners, collaborators, hosts for ESR and ER placements, teachers, or external advisors of the network.[1]

Overall, the network has been quite a success. It has delivered training and research in a serious, yet thoroughly enjoyable manner and has covered many aspects of science and science-related subjects, including highlights such as communication, Intellectual Property and commercialization, epistemology, Bioethics, Science and Society, and Science and Arts. One of the highlights of the network was the mobility of ESR and ER across Europe. Research placements in host laboratories abroad were daily network business, turning many investigators not only into excellent scientists, but into cunning linguists at the same time. These activities are reflected in the considerable output of the network. "RedCat" has already generated an impressive number of—often jointly authored—publications and forged many long-lasting scientific cooperations and personal friendships. It has also lived up to its promise to train a good number of emerging scientists who are now actively pursuing their independent research careers.

In any case, all ESR and ER have passed their rites of passage to independent scientists. They now know how to "lead the dog so it does not crap on its leash", as Claus Jacob metaphorically says after successful PhD—or Diploma—vivas.

While the "RedCat" spirit—and the "RedCat" website—are still alive, and "RedCat" publications are presently extending the literature on natural products and biological aspects of redox active substances, some of the "Cats" have moved on and diversified in new networks, such as the Interreg IVa network "Corena" covering the Saarland, Lorraine, and Luxembourg or a new graduate training network "NutriOx" which now exists between the Universities of Saarland, Burgundy, and Lorraine.

This book is a fine summary of some of the most successful "RedCat" activities. Indeed, many of the chapters have been co-authored by the

[1] "RedCat" stands for *red*ox *cat*alysis. It describes an Initial Training Network for early stage and experienced researchers funded under the Framework 7 'People' program of the European Union (Grant Agreement No 215009, Natural Products and related Redox Catalysts: Basic Research and Applications in Medicine and Agriculture). The web page is available using the following url: http://www.redcat-itn.eu/.

network's own ESR and ER. To them, the book will provide a lasting memory of the fantastic times they had while being turned into the scientists of the future. For the coordinator and some of the supervisors, the book will raise fond memories of a very special time when massive science and mental sickness were closer together than ever before (and after).

The basis for this special interest may be found in human cell physiology, which is rich in redox related processes. Research during the last couple of decades has demonstrated that cellular redox processes are of paramount importance, not only in the context of energy metabolism but also regarding the overall 'well-being' of the cell and organism as a whole. Disturbances in the intracellular redox balance, for instance in form of oxidative stress (OS), may disrupt normal cellular function and ultimately cause severe damage to the cell (the latter may undergo apoptosis), tissue, and organism affected. Indeed, for several decades, OS has been considered as a major cause of many human diseases, including auto-inflammatory and neurodegenerative diseases, diabetes, glaucoma, and cancer to mention just a few. While such a simple causal relationship between OS and human diseases no longer holds true, it is safe to state that many human disorders and ailments are directly or indirectly associated with a disturbed intracellular redox balance. At the same time, it has become apparent that redox processes are not only at the root or a consequence of disease, but also play a vital and thoroughly beneficial role in healthy cells, tissue, and organisms. In a more subtle manner, cellular redox events are indeed involved in widespread cellular signaling, regulation, and control processes. In fact, some of the early studies in the field of cellular redox regulation have even linked major cellular 'life and death decisions', such as proliferation, differentiation, and apoptosis to the cytosolic electrochemical potential regulated by the glutathione/glutathione disulfide (GSH/GSSG) redox pair.

More recent studies have refined this model by considering cellular redox events at a molecular level, for instance in form of oxidative protein modifications. Within this context, the oxidation of cysteine residues in proteins appears to play a major role. Various studies have highlighted the special impact that oxidative cysteine modifications, such as *S*-thiolation, disulfide, or sulfenic formation have on protein function and enzyme activity—and subsequently also on cellular processes, such as cell signaling. Not surprisingly, a number of new and often still speculative concepts and hypotheses have been postulated during the last couple of years to address this unique intracellular sulfur redox network, and some of them, such as the 'cellular redoxome', the 'cellular sulfenome', and the 'cellular thiolstat', will be discussed briefly as part of Chap. 9.

At the same time, there have been various attempts to control such cellular redox processes by endogenous compounds. Most obvious, perhaps, is the widespread and sometimes almost excessive use of so-called antioxidants, i.e., compounds that apparently counteract OS and hence somehow may protect cells, tissues, and even the whole organism against oxidative damage. Such antioxidants feature prominently, for instance, in fruit juices, lemonades, tea bags, mueslis, and anti-aging, anti-wrinkling skin crèmes where they are said to provide an extra benefit to the consumer. Such antioxidants are almost exclusively derived from edible (parts of) plants, which is hardly surprising, as such compounds are usually readily available and in many respects safe for human consumption or at least for topical applications. They include some of the usual suspects, such as vitamins A, C, and E, a couple of coenzymes, flavonoids, and organic sulfur compounds, which will be discussed later on in this book as part of individual chapters. While the current hype surrounding the practical uses of such antioxidants as chemopreventive, anti-aging, anti-inflammatory, or even anticancer agents is often not fully justified from a purely scientific perspective, antioxidants in food and food supplements are a hot topic in research and represent a rapidly expanding market for a wide range of new products. Bearing in mind that the aging organism is marred by OS and a loss of natural antioxidant defenses, the full potential of antioxidants in an aging society becomes apparent.

The various issues associated with such antioxidants are manifold, complex, and diverse, and range from the more or less problematic labeling of certain food products with ORAC (Oxygen Radical Absorbance Capacity) values and the marketing of antioxidant food supplements for the elderly to the use of antioxidants as free radical scavengers in anti-aging skin crèmes and cosmetics. Within this context, one must bear in mind that the size of the antioxidant market is enormous, and a range of entirely new products (and associated manufacturing processes) have been emerging in this field, which go well beyond the traditional antioxidant vitamin preparations or ACE juices (see also Chap. 2). These developments may be exemplified by the sudden use of grape seeds for the manufacture of grape seed flour: The latter is rich in polyphenols and has turned a former waste product (i.e., grape seeds) into a hitherto rarely considered product and—economically speaking—into a gold mine, which has already made its way into most households in the form of quite common products, such as grape seed flour-enriched pasta.

This simple example of polyphenol-rich grape seed flour as 'green gold' highlights the huge impact redox active secondary metabolites currently exert on nutrition, research, economics, and society as a whole. Not surprisingly, there are other secondary metabolites besides the polyphenols which already play a similar role in society or are likely to acquire a certain importance soon. As part of this book, we will consider a range of such rather promising natural products, for instance as part of Chap. 6. In doing so, we will focus on the chemical properties, biochemical actions, and biological activities which may (or may not) justify such a practical use. Importantly, our discussion will not be driven by or limited to the usual antioxidants, such as certain vitamins or flavonoids, but will endeavor to explore a range of different, often less known antioxidants, forming a scientific perspective on equally interesting, emerging redox active secondary metabolites. Some of these compounds, such as the organic sulfur compounds (OSCs), exhibit extraordinary biological activities and open up potential applications in the field of medicine and agriculture, which go well beyond a traditional antioxidant or chemopreventive activity. Other compounds, such as xanthohumol or certain natural isothiocyanates, even seem to influence epigenetic events and hence contribute to the emerging field of nutri-epigenetics. In contrast, various oligomeric and polymeric metabolites, such as the proanthocynanidins and tannins, are not only redox active but also associate with proteins and enzymes, an interaction that may ultimately result in antimicrobial activity and may even contribute to a reduced calorie uptake in the gut.

These examples should be sufficient to demonstrate that this book on secondary metabolites is not just yet another compilation of traditional plant products or antioxidants. We will rather consider redox active secondary metabolites from various scientific perspectives, including their identification, chemical analysis, and isolation, their biosynthetic pathways and synthesis in the laboratory as well as their biological activity, biochemical mode(s) of action and practical applications. Here, we will also pay tribute to modern nano-technological methods able to improve bioavailability and witness how a natural product, such as a garlic extract, can be turned into a commercial success story. This facet-rich agglomerate of newly emerging themes requires specialist knowledge from diverse disciplines, including plant biology, bioanalytics, synthetic chemistry, cell biology, medicine, agriculture, and economics. We have therefore recruited a number of internationally renowned experts who have kindly contributed their in-depth knowledge and experiences to individual chapters of this book. As a result, the contributors are able to discuss a wide range of selected topics related to redox active secondary metabolites from vastly different, and often unusual and exciting angles—and with the kind of in-depth knowledge which is clearly required as part of a serious scientific discourse. While this book cannot serve as a complete or ultimate encyclopedia listing all known redox active natural products, it aims to highlight some of the most recent and exciting developments in the field in order to stimulate future research.

First, we will therefore take a more historic perspective on the ‘antioxidant story’, its basis, main notions, and lessons for the present and the future. Here, Agnieszka Bartoszek from the Gdansk University of Technology will argue that the idea of antioxidants as agents beneficial to human health has developed from an initial, perhaps premature hypothesis to a more sophisticated biochemical regulatory concept which is changing human nutritional behavior and lifestyle to the better. These conceptual changes over the last decades also provide a fertile ground for more speculative and innovative approaches to redox active secondary metabolites which will be discussed in many of the subsequent chapters.

We will continue with a closer look at the identification and characterization of natural substances using cutting-edge analytical techniques. One chapter contributed by Patrick Chaimbault from the University of Lorraine in France will consider recent advances in employing techniques such as mass spectrometry for the identification of natural substances. During the last decade, such techniques have developed at a breathtaking pace, and it is now possible to identify certain plant metabolites even in intact plant materials.

After a closer look at the bioanalytical methods currently available for the identification of secondary metabolites, we will turn our attention to the various biological activities—and possible practical applications—which have been associated with these products during the last decade or two. Here, we will first explore the true meaning of 'redox activity', especially in the context of antioxidant activity and redox modulation. This chapter, contributed by Torsten Burkholz and Claus Jacob from the University of Saarland in Saarbruecken, Germany, will infuse concepts of (redox) chemistry into the biochemical debate in order to resolve some of the myths of biological redox chemistry. We will, for instance, differentiate between simple chemical oxidizing or reducing agents and subsequent cellular pro- or antioxidant responses. We will also provide a brief discussion on the hot issue of the ORAC value.

Equipped with these more fundamental insights we will then turn our attention to the vast and often misty field of OS, antioxidants, chemoprevention, and some of the surprisingly beneficial roles ascribed to pro-oxidants. Contributed by Lars-Oliver Klotz from the Friedrich-Schiller-University, Jena, this chapter will provide a critical view of some of the notations commonly associated with antioxidants. It will reject the rather outdated view of antioxidants as 'good' and oxidants as 'bad' species and promote a more differentiated view, which is based on subtle cellular redox signaling and regulatory events affected and fine-tuned by pro- as well as antioxidants. Ultimately, both pro- and antioxidants may be equally beneficial or detrimental, depending on the specific situation and circumstances and, of course, the amounts consumed.

This more general chapter is followed by three contributions which discuss individual redox modulating natural compounds. Each of these chapters, and the compounds discussed therein, represents a particular aspect of redox active secondary metabolites which is of considerable interest to human nutrition, yet is based on entirely different underlying biochemical processes. This parade of selected natural compounds will begin with flavonoids and stilbenes, compounds that occur in many fruits and berries and seem to exert protective effects on the human body, such as the ones commonly implicated in the "French Paradox". Contributed by Artur Silva and colleagues from the University of Aveiro in Portugal, this particular chapter will build the bridge between the natural compounds found in plants and their potential uses on the one hand, and the ability of synthetic chemists to produce such natural substances as well as their tailor-made derivatives in high amounts and excellent purity in the organic synthesis laboratory.

While this chapter focuses on the chemistry and biological activity of natural compounds involved in the "French Paradox", the subsequent chapter by Norbert Latruffe and his colleagues from the University of Burgundy at Dijon, France, takes a closer look at the various health benefits associated with the stilbene compound resveratrol, which is found in grapes and grape products, especially in red wine. This chapter reviews the latest literature in order to assess if the consumption of red wine may indeed protect from cardiovascular or inflammatory diseases.

As inflammation is commonly associated with a sharp increase in reactive oxygen and reactive nitrogen species (ROS and RNS), it is hardly surprising that many redox active natural products have been associated with anti-inflammatory effects in the past. Here, polyphenolic compounds, such as colorful proanthocyanidins found in many fruits and berries, are of particular interest. Chapter 8 contributed by Hadi Ebrahimanijad from the Shahid Bahonar University, Kerman, Iran together with Claus Jacob and his team (Saarbruecken) will therefore take a closer look at oligomeric and polymeric substances, such as the polyphenolic proanthocyanidins. The latter feature a range of emergent properties which are the direct result of the oligo- and polymeric character of the compounds and cannot be found in the monomeric counterparts. Besides exhibiting a powerful redox behavior due to the presence of a multitude of redox centers in these polymers, these substances are also able to non-covalently interact with proteins and enzymes. The resulting inhibitory effects on proteins and enzymes are highly interesting, for instance, from the perspective of antimicrobial activity and in the context of the control of digestive enzymes.

After highlighting the importance of some of the nutri-chemicals for human health, and discussing the (bio-)chemical basis of such activities, the reader's attention will then be turned to more practical applications of redox active secondary metabolites and the plant products in which they are present. Here, our focus will reside with organic sulfur compounds. Despite often being grouped together by natural product scientists, OSCs are chemically extraordinarily diverse and associated with a wide range of activities and possible applications in medicine and agriculture. In order to understand why many OSCs are highly, yet often also selectively active in biological systems, we will first need to consider their specific, sulfur-based reactivity and how this reactivity relates to specific cellular targets, such as the network of cysteine proteins which together form the 'cellular thiolstat'. After this brief and more general overview of sulfur-based biological redox systems and some of their modulators, which is presented by Martin Gruhlke and Alan Slusarenko, the team from the RWTH Aachen will take us on a journey to the intricate and often rather surprising chemistry of thiosulfinates and polysulfanes—and how this chemistry translates into biological activity and possible applications in medicine and agriculture. Subsequently, Chris Hamilton and his colleagues from the University of East Anglia will introduce us to bacillothiol and mycothiol, two bacterial thiols that have emerged as potential targets of novel, thiol-modulating antibacterial agents. Besides proposing new targets for therapeutic redox modulation, this chapter underlines the importance of thiol-based cellular redox systems in various organisms and showcases promising avenues for a more or less selective attack at such thiol-containing molecules.

The subsequent chapter is written by Awais Anwar and his colleagues from the British company ECOSpray Ltd., which during the last decade has developed a range of interesting garlic-derived products for applications in the field of eco-friendly agriculture. Awais and his colleagues discuss the value and potential uses of such natural materials, and how a simple agricultural product such as garlic can be turned into a commercially viable and ecologically sound product.

The section on OSCs and their potential uses is followed by a fine selection of chapters that try to push the boundaries of redox active natural product research to new limits and to open up new applications for such compounds.

As part of this section, we will consider several cutting-edge approaches to generate new compounds or to turn existing products into new 'forms' which enable practical applications. The first chapter of this section, contributed by Peter Olofson from Redoxis AB in Sweden and his colleagues from Sweden and Denmark, considers a rather simple yet effective means of ‘processing’ an existing natural product, in this case chlorophyll, into a new compound with potential practical application. Indeed, the production of phytol from chlorophyll by digestion in herbivorous animals represents an elegant and, at the same time, traditional means of unlocking the potential of natural products and developing new ones. While phytol in itself is not redox active, it nonetheless seems to influence various cellular processes that ultimately may also regulate redox events involved in inflammation. This chapter is followed by several other contributions which consider more eloquent biotechnological, clinical, and nanotechnological approaches. The chapter contributed by Frédéric Bourgaud from the University of Lorraine illustrates the more biological avenue, which considers the biosynthetic pathway of a natural product, in this case a novel furanocoumarin. Once the enzymes involved in the biosynthesis of such a molecule are known, it is, in principle, possible to fine-tune the structure of the natural product my mutation of the biosynthetic machinery. The subsequent chapter by Gilbert Kirsch and colleagues (Metz), in contrast, chooses a more chemical approach which starts with the synthesis of coumarin derivatives and ultimately generates tailor-made derivatives in the form of natural product hybrid molecules.

The final chapter of this section provides a third angle to custom-made natural products especially with regard to solubility and bioavailability. Rather than modifying the chemical structure of the molecule, however, the approach described by Cornelia Keck and Karl-Herbert Schaefer from the University of Applied Sciences in Kaiserslautern, Germany, considers the size of the natural product particles. Here, nanotechnology opens the door to a whole new field of natural product research as it endows good solubility and bioavailability to a range of otherwise difficult to use natural products. To date, the practical applications of the ‘non-nano’ forms of these products have been limited by the poor solubility and hence limited efficacy in complex organisms, including in humans.

Importantly, the notion of redox active natural products is not limited to small molecules. Redox active enzymes also play an increasing—and increasingly diverse—role in chemistry, biotechnology, and medicine. The final two contributions therefore consider practical uses of redox active enzymes. The chapter by Jennifer Littlechild and colleagues from the University of Exeter in the UK reviews the properties and practical uses of certain haloperoxidases in industrial-scale chemical synthesis. The chapter by Peter Meiser and colleagues from Ursapharm Arzneimittel GmbH in Guedingen, Germany looks at the Bromelain enzymes derived from pineapple as a powerful enzyme cocktail used against injuries and inflammation.

After this exciting encounter with some of the still more speculative, yet clearly cutting-edge approaches and technologies in natural product research, it will be time to summarize the current state of this field of research and to provide a brief outlook on imminent potential developments. Here, the scientific perspective is clearly important, yet it cannot be considered in isolation and without paying suitable attention to the ongoing changes in society, medicine, and nutritional habits, as well as to agricultural demands and emerging economic niches. So there is our summary of the journey provided by this book—enjoy!

Authors Biography

Claus Jacob (born 1969) has been trained as a synthetic (in)organic and biological chemist at the Universities of Kaiserslautern, Leicester, Oxford, and Harvard. He graduated with a 1st class B.Sc. (Hons.) degree from the University of Leicester in 1993, and with a D.Phil. from the University of Oxford in 1997 ("Genetic engineering of redox active enzymes", supervisor Prof. Allen Hill FRS). He subsequently joined the institute of Prof. Bert Vallee at Harvard Medical School as a Feodor Lynen Fellow (Alexander von Humboldt-Foundation) to study processes controlling intracellular zinc homeostasis. During this time, he also obtained a Magister Artium degree in Philosophy, History, and Psychology from the University of Hagen in Germany (M.A. dissertation on Protochemistry as constructivist foundation of chemistry). He left the US in 1999 to spend some time with Prof. Helmut Sies at the Heinrich-Heine-University in Duesseldorf, Germany, as part of a BASF Research Fellowship from the German Merit Foundation.

Claus started his independent scientific career as lecturer at the University of Exeter in the UK in 1999 and in 2005 moved to the University of Saarland where he currently holds the position of Professor of Bioorganic Chemistry. Claus is an expert in redox active compounds and their impact on biological systems and to date has published over 100 publications in this field. Over the years, his research has focused on Reactive Sulfur Species (RSS) and the cellular thiolstat, terms his team has introduced in 2001 and 2010, respectively. Besides his strong interest in redox active sulfur, Claus has also developed an active research program on synthetic 'sensor/effector' redox modulators based on selenium and tellurium, on redox active plant metabolites and on nanoscopic redox particles. His research includes synthetic and analytical chemistry, biological activity studies and 'intracellular diagnostics' to decipher and map out intracellular events and mode(s) of actions. Claus has coordinated the EU Marie Curie Initial Training Network "RedCat" (2008–2012), has been a partner in the technology transfer project "Corena" (2009–2012) and is currently partially in charge of the natural products project "NutriOx".

Throughout the years, Claus has undertaken many projects to become a highly skilled undertaker, but never a true philosopher, yet his more philosophical and cunning linguistic outpourings are famous and he still maintains a keen interest in various aspects related to the philosophy of chemistry.

Torsten Burkholz (born 1979) has been trained as an inorganic and medicinal chemist at the University of Saarland in Saarbruecken, Germany, graduating with a German "Diplom" in Chemistry. After completing his PhD studies at the University of Saarland in the fields of Chemistry and Pharmacy under the supervision of Prof. Claus Jacob in 2010, he joined the European Marie Curie Initial Training Network "RedCat" as postdoctoral Experienced Researcher, conducting research in the field of Cell Biology in the group of Prof. Paul G. Winyard at the Peninsula College of Medicine and Dentistry, Exeter, UK. In 2012 Torsten moved back to the University of Saarland where he currently holds the position of an "Akademischer Rat" in Bioorganic Chemistry.

As part of this senior position, Torsten is managing the research laboratory of Bioorganic Chemistry, as well as the relevant teaching and the examinations of undergraduate students. Together with Prof. Claus Jacob, he has to date published over 30 publications in the field of oxidative stress, chalcogen containing natural compounds, and their biological activity and, more recently, on the cellular thiolstat. Torsten's ongoing research includes synthetic and analytical chemistry, biological activity studies, and 'intracellular' diagnostics.

In 2013, Torsten was appointed as Visiting Professor at the University of Applied Sciences Kaiserslautern, where he is lecturing Pharmacology. In the same year, he established his own small company named "Dr. Burkholz Life Science Consulting UG" which provides scientific consultations for small and medium-sized companies in the field of nutrition, food supplements, and natural compounds. His company also offers training and consulting in Inorganic and Analytical Chemistry, as well as in Physics and Pharmacology.

Gilbert Kirsch (born 1947) has been trained as an organic chemist at the Universities of Strasbourg and Metz. He started his academic career in 1973 at the University of Metz (now University of Lorraine) where he currently holds the position of Professor of Organic Chemistry. He has been a postdoc at Oak Ridge National Laboratory (TN) in the Nuclear Medicine Group and was also an invited scientist at Kodak (Rochester, NY) as well as invited professor at the University of Minho (Portugal) and Emory University (Atlanta, GA).

Gilbert's interests reside in heterocyclic chemistry, especially in the field of five-membered aromatic systems (thiophenes, selenophenes, tellurophenes, thiazoles, selenazoles) and their benzo-condensed derivatives. Lately, he developed synthetic work in the field of coumarins, looking at biological activities (CDC25 phosphatase inhibition). From his research, he published over 200 papers, wrote different chapters in books, like Patai's Functional Group Series, in Houben-Weyl, in Chemistry of Heterocyclic Compounds (J. Wiley Interscience), and in Springer's Selenium and Tellurium Chemistry. He holds also few patents in the field of heart imaging and sulfur-containing tire additives. Gilbert has coordinated an Interreg program (acronym "Corena") on natural compounds for Medicine and Agriculture, and has participated in the EU ITN Marie Curie program "RedCat". He is participating in the regional programs Bioprolor and Biocaptech and in a national French ANR program on *para*-hydrogen.

Alan Slusarenko is Head of the Plant Physiology Department at RWTH Aachen University. His research has centered on resistance mechanisms of *Arabidopsis* to infection and more recently on Natural Products in Plant Protection. Alan obtained a PhD in Plant Pathology from Imperial College in 1981 and was a lecturer in the Department of Plant Biology at Hull University in the UK from 1983 until moving in 1988 to an Assistant Professorship in Molecular Plant Pathology at the University of Zuerich in Switzerland and subsequently in 1995 to the Chair of Plant Physiology at RWTH Aachen in Germany.

Paul Winyard is Professor of Experimental Medicine at the University of Exeter Medical School (formerly Peninsula College of Medicine and Dentistry), Exeter, UK, where he has been based since 2002. Previously, he held the same title at St Bartholomew's and the Royal London School of Medicine and Dentistry, London, and was a Visiting Professor at the University of California, San Francisco (2000–2001). Paul originally trained as a biochemist, and his current research interests center on the role of oxidative/nitrative stress and redox signaling in chronic inflammatory diseases such as rheumatoid arthritis. Paul leads an internationally recognized research group, having published over 200 research papers in the field of oxidative stress in inflammation. In particular, his research has focused on the development of novel free radical-related assays and therapeutic strategies, and the translation of these developments into clinical diagnostic assays and pre-clinical and early-phase clinical studies.

Paul is a co-inventor in relation to seven patents, and is a Senior Editor of the *Journal of Inflammation*. He is also a member of the editorial boards of *Redox Biology*, *Frontiers in Oxidant Physiology, Frontiers in Inflammation, Current Pharmaceutical Design* and the *Open Inflammation Journal*. He is a committee member of the *British Inflammation Research Association* (*BIRAs*), and serves on a number of UK and European research grant awarding committees.