Oxidative Stress in Applied Basic Research and Clinical Practice

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Redox-Active Therapeutics

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Foreword

Free Radical and Redox Biology in Disease States: The Era of Redox-Active Therapeutics

Free radicals and oxidant species have been associated with the initiation and progression of several disease states for the last three decades. Disruption of cell and tissue redox homeostasis occurs by a variety of molecular mechanisms including the alteration of mitochondrial function, overactivation of membrane-bound NAD(P)H oxidases, induction or uncoupling of nitric oxide synthases, redox cycling of xenobiotics, mobilization of iron pools, and enhanced activity of xanthine oxidase, myeloperoxidase, and other “redox” enzymes in specific cell types and tissue regions. These sources of reactive species have been identified as culprits of creating pro-oxidant environments that facilitate oxidative molecular damage. Additionally, oxidants, at controlled levels, have been more recently shown to participate in redox signaling pathways. Overall, significant changes in steady-state concentrations of reactive species can have a profound impact on the control of metabolism and gene expression. Two major challenges in the field have been to (a) dissect and prove the relevance of different oxidative processes in the pathophysiology of disease (in spite of its association) and (b) develop rational and effective redox-active therapeutics that can neutralize molecular events of disease. In one way, a + b are intertwined because current evidence is indicating that effective redox-active therapeutics should be targeted towards the main participating routes/reactive species and/or cell/tissue compartments. Additionally, a successful redox-based intervention serves as a “proof of concept” to connect oxidative processes to pathology. In the last decade a great deal of progress has been made on the sound development of such redox-active therapeutics. For example, in the case of transition metal-based synthetic compounds, modulation of the redox potential, structure, and hydrophobicity have largely improved the pharmacological action of these compounds by means of the efficient elimination of reactive species due to optimized kinetic capacity and biodistribution, together with a decrease of undesired interactions with biomolecules. Important findings through the years have been that

many of the developed redox-active compounds are multifunctional in terms of both coping with a group of reactive species and catalytically participating in redox detoxification pathways at the expense of reducing equivalents obtained from endogenous reductants (such as uric acid, ascorbate, or glutathione) or even from redox enzymes or the mitochondrial electron transport chain. The high kinetic efficiency of some of the compounds together with catalytic character of these reactions makes it possible to have potent actions in the presence of micromolar or submicromolar amounts, with little or negligible associated toxicity.

Another important aspect, successfully developed lately to increase pharmacological actions, relates to the improved subcellular distribution. Indeed, targeting of redox-active compounds to specific cell compartments such as mitochondria by a variety of chemical modifications to the parent moiety has revealed to be a key breakthrough. Indeed, targeted compounds have been shown to increase their concentrations in specific intra- or extracellular compartment several hundreds of time, which has resulted in higher specificity and effectiveness.

Additionally, other important related conceptual demands (and challenges) have emerged lately in the development and testing of redox-active therapeutics. Firstly, many times the observed protective biological effects exceed what can be expected from carefully contrasting the actual concentrations of redox-active compound achieved intracellularly with the known rate constants of reaction with reactive species (important to say that the latter have been typically obtained in homogenous solutions, not in the crowded and compartmentalized cellular environment); indeed, it is not always obvious to visualize how some of the utilized compounds may largely outcompete the many parallel reactions of reactive species with critical intracellular targets or significantly augment pre-existing antioxidant capacities (e.g., how much could an “SOD mimic” increase SOD activity *in vivo*, when 10–20 μM SOD is present in different cellular compartments and react at near diffusion-controlled rates with superoxide radicals!). Part of the answer seems to rely on the capacity of these compounds to eliminate a variety of species, but *also* in their capacity to induce antioxidant responses at the transcriptional level (presumably via oxidation reactions involving protein thiols or maybe even iron-sulfur clusters) that ultimately results in the upregulation of endogenous antioxidant systems. Indeed, it is increasingly recognized that redox-active compounds may activate redox-sensitive transcription factors that, in turn, trigger cytoprotective gene responses. Thus, direct detoxification reactions may run simultaneously with more subtle and permanent changes in cell/tissue antioxidant capacities.

In the past, studies on different human pathologies administering both natural and synthetic compounds have been executed, suggesting positive pharmacological actions. Unfortunately, some of the promising studies carried out on small and controlled human populations were not confirmed later in studies with more demanding standards and/or on larger populations, which signified a large delay for the field of redox-active therapeutics and medical practice, and challenged the view on the role of disruption of redox processes on the basis of human disease conditions. But further scientific progress was made over the last decade both on the understanding of free radical/redox processes participating in molecular basis of disease and the

design of synthetic redox-active compounds with improved chemical reactivity, selectivity, and biodistribution. Indeed, I firmly think that after the initial enthusiasm followed by a drawback experienced with redox-active therapeutics in humans, the field is now on a new and wide avenue of solid development, which is likely to become clinically successful. With the more profound understanding of the subtle redox reactions, mediators, and processes underlying the development of pathologies and the rationale design of more suitable synthetic compounds with enhanced selectivity, reactivity, and compartmentalization, the application of redox-active therapeutics to the clinical arena is getting very close. These new therapeutics are expected to be useful in inflammatory, cardiovascular, and neurodegenerative conditions and in radioprotection, among several other disease states. In addition to the large amount of existing preclinical data, some of the newer compounds are or will be promptly tested in clinical trials. Obviously, a positive pharmacological outcome will be of great impact to the field and to medical therapeutics.

All the key aspects of the field of redox-active therapeutics are nicely covered in this book edited by Drs. Batinić-Haberle, Rebouças, and Spasojević. A nice progression from very basic concepts and observations (starting with chapters from the discoverers of superoxide dismutase, Irwin Fridovich and Joe Mc Cord) to the application of redox-active therapeutics in large range of disease conditions is presented in a fully updated and coherent manner. With their vast experience in the field, the editors have been able to assemble an outstanding group of chapters written by leading investigators. This book represents a large and most welcome effort to bring together, and with a profound and solid view, the current developments and potential applications of redox-active therapeutics for the treatment of human pathologies. The work also leaves open the possibility for further research in the area including a deeper understanding of the pharmacological mechanism of redox-active drugs *in vivo*, identification of novel molecular targets and salutary mediators, development of tailored drugs for enhanced selectivity, and application of the more promising compounds for acute and chronic disease conditions in humans. I warmly congratulate the editors and authors for the outstanding work and I am positive this book, a very first dedicated to stress the key role of redox-active therapeutics in medicine, will constitute a reference material both for the free radical/redox biomedical community and for any biomedical and chemical researchers interested in the role of free radicals, oxidants, and antioxidant systems in human health and pathology.

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Preface

The inauguration of this book marks ~ half a century since the inception of the field of Free Radicals in Biology and Medicine with the seminal discovery of the major endogenous antioxidative defense, Cu,Zn superoxide dismutase enzyme (Cu,ZnSOD), by Irwin Fridovich and Joe McCord in 1969 [1].

The discovery of Cu,ZnSOD was followed by discoveries of mitochondrial (MnSOD) and extracellular (Cu,ZnSOD) isoforms. The subsequent studies of Babior et al. [2] supported the biological relevance of superoxide ($O_2^{\bullet-}$) demonstrating that this radical is formed, as a part of antibacterial strategy, by the action of NADPH oxidases in white blood cells. Over years it has been demonstrated that a number of enzymatic systems, oxidases, oxygenases, nitric oxide synthases, complexes I and III of mitochondrial respiration, and others produce $O_2^{\bullet-}$ (intentionally or not) and subsequently and rapidly H_2O_2 (enzymatically or not) under physiological and pathological conditions. Throughout half a century of research, immense knowledge has been collected on free radicals and other reactive species demonstrating their critical roles in redox biology of healthy, metabolically stressed and neoplastic cells. This in turn has inspired numerous studies that explore therapeutic approaches, many of which are covered in this book, to normalize physiological redox status in normal but diseased cells and induce apoptosis of cancer cells.

Ten years after the discovery of the SOD enzyme, the first study on an SOD mimic was reported by Pasternack and Halliwell [3]. The authors demonstrated the SOD-like activity of an Fe porphyrin. In the early 1980s Archibald and Fridovich [4] showed that Mn salts, such as Mn(II) lactate, possess high SOD-like activity thereby justifying the existence of organisms that accumulate mM levels of Mn to overcome their lack of an SOD enzyme. The first report on the Mn salen class of SOD mimics (EUK-8) appeared in 1993 [5]. One of those, EUK-134, is in use as an active ingredient in sunscreen products. Meanwhile Irwin Fridovich's group embarked on decades-long development of porphyrin-based SOD mimics. A highly efficacious Mn porphyrin-based SOD mimic was reported in 1997 by Ines Batinić-Haberle [6], setting the stage for the design of multiple redox-active metalloporphyrins on the basis of structure-activity relationships. In parallel with Mn porphyrin-based SOD mimics, works by Dennis Riley's group [7] gave rise to the

Mn(II) cyclic polyamine (aza-crown ethers) class of potent SOD mimics. Compound leads from both porphyrin and polyamine classes of SOD mimics are presently in clinical trials as radioprotectors of normal tissue. While not SOD mimics, in the early 1990s the redox-active (non-metal based) nitrones and nitroxides have been developed as therapeutics [8]. The OKN-007 nitrone (also known as NXY-059) went through clinical trials for stroke and is presently in a clinical trial as an anti-cancer therapeutic for recurrent malignant glioma. The redox-active quinone-based compound, MitoQ, has been in clinical trials for Parkinson's disease and for chronic hepatitis C and is presently used for skin care. In the late 2000s "shrunk" porphyrins, metallocorroles, emerged as prospective SOD mimics and therapeutics [9]. Numerous other redox-active metal complexes and SOD mimics were developed as therapeutics by different groups, some of which are addressed in this book. The wealth of data collected thus far demonstrates that structure-activity relationships, initially developed for Mn porphyrins, are valid for different classes of SOD mimics. The photosensitizing porphyrin ligand, $H_2TM-4-PyP^{4+}$, is being incorporated into nano-scaffolds to form nano-phototheranostics for diagnosis and treatment of various cancers. As alternatives to such photosensitizers, quantum dots made of semiconductor metal-containing materials (such as CdSe, CdTe, and InAs) conjugated or not to Zn(II) porphyrins have been explored [10].

Since the discovery of SOD enzymes, tremendous progress has been made on the chemistry of small endogenous reactive species and enzymes which maintain the balanced redox environment of a normal cell; the perturbed balance results in a pathological condition known as oxidative stress. Different classes of SOD mimics were initially developed and anticipated to be specific to $O_2^{\bullet-}$. It might have been obvious from the very beginning that such small molecules (relative to a protein-structured enzyme), with biologically compatible reduction potentials, would react with numerous reactive species. Yet, the wealth of knowledge on the chemistry of those species was not available to allow for such "free" thinking. Moreover the biological importance of numerous species such as nitric oxide, peroxynitrite, nitroxyl, carbon monoxide, reactive sulfur, and selenium species and their cross-talk has not yet fully emerged. In turn, not until the end of the 1990s and early 2000s did the rich reactivity of SOD mimics and other redox-active therapeutics towards species other than $O_2^{\bullet-}$ surfaced.

Researchers have often incorrectly assigned the effects of redox-active drugs to particular reactive species. The unselective chemistry of such compounds, the multitude of reactive species involved, and the biological milieu are too complex to define the mechanism of action with certainty. The use of genetically modified animals or microorganisms has allowed progress. While insight into the redox biology of a cell and redox-active compounds is expanding, the actions of compounds are still often incorrectly singularly attributed to the dismutation of either $O_2^{\bullet-}$ or/and H_2O_2 , when neither a true SOD mimic nor a functional catalase mimic is used. A recent comprehensive study pointed out that the majority of metal complexes (various Mn or Fe porphyrins, Mn salen EUK-8 or Mn(II) cyclic polyamines such as M40403) are not catalase mimics [11]. Only Fe(III) corroles have modest catalase-like activity, and its biological relevance awaits further exploration. Another

important issue with any drug is its purity. Caution needs to be exercised, as commercial suppliers have frequently sold impure compounds, which in turn have hindered correct discussions of the effects observed.

It was not until the mid-2000s that evidence was provided to demonstrate the interaction between redox-active therapeutics and transcription factors, such as HIF-1 α , AP-1, SP-1, and NF- κ B. Effects on transcription factors have been found with different classes of therapeutics, both synthetic and natural, such as Mn porphyrins, nitroxides, Mn salen derivatives, sulforaphane, flavonoids, and polyphenols. Initially, it was speculated that the effects were due to the ability of Mn porphyrins to rapidly remove reactive species, produced upon oxidative stress, which would have otherwise activated one or more transcription factors and in turn transcription of a group of genes. It took nearly a decade before it became clearer that at least one of the major mechanisms involves protein thiols. This learning process required joint efforts of chemists, biochemists, pharmacologists, and biologists.

For years, an obvious fact was overlooked. Catalysis of O₂^{•-} dismutation is efficacious *ONLY* if a mimic (or SOD enzyme) is an equally good oxidant and antioxidant, i.e., it equally well oxidizes O₂^{•-} to oxygen and reduces it to H₂O₂. Thus an SOD mimic and/or SOD enzyme can act in vivo both as an antioxidant and (pro)oxidant. Moreover, the reduction of O₂^{•-} by an SOD mimic gives rise to an oxidant—H₂O₂. At that point it was a common understanding that H₂O₂ cannot accumulate in the cell as it is eliminated by numerous (redundant) enzymatic systems such as catalase, glutathione peroxidases (GPx), and peroxiredoxins. Only recently has it emerged that those systems may be downregulated and/or inactivated during disease, which would in turn lead to H₂O₂ accumulation—a frequent scenario in cancer. While the SOD enzyme is a tumor suppressor in healthy cells, under disease conditions, the SOD enzyme may become a tumor promoter. Such reports coincide with the conclusion that indeed an SOD mimic, with redox properties similar to SOD enzyme, can function as either a pro- or antioxidant depending upon the local environment.

Jon Piganelli was the first to suggest that, in diabetes models, Mn porphyrin can act as an oxidant, possibly oxidizing the p50 subunit of NF- κ B in nucleus [12]. The notion was supported by a pharmacokinetic study on macrophages which showed that Mn porphyrin accumulates threefold more in the nucleus than in cytosol. A crucial study on lymphoma cells by Margaret Tome and her colleagues [13] furthered Piganelli's notion in helping understand which reactions are likely involved in the suppression of NF- κ B transcriptional activity. Tome showed that H₂O₂ and GSH are indispensable in the actions of a redox-active Mn porphyrin in oxidatively modifying—S-glutathionylating—p65 and p50 subunits of NF- κ B. Once glutathionylated, NF- κ B cannot bind to DNA to initiate gene transcription. S-glutathionylation was then demonstrated by Tome's group to occur with other thiol-bearing proteins including mitochondrial complexes I, III, and IV. The inactivation of complexes I and III resulted in the suppression of ATP production. An effect of Mn porphyrin on glycolysis was also seen, possibly involving S-glutathionylation reactions. Importantly, no toxicity was observed with normal lymphocytes. Mitochondrial accumulation of Mn porphyrins and comprehensive aqueous chemistry on cysteine oxidase and/or GPx-like activity of Mn porphyrins by Batinić-Haberle and her

colleagues supported such observations. Studies point to a major role of H_2O_2 in the actions of Mn porphyrins and agree well with a growing recognition of the critical role of this species in cell biology. A similar mechanism of action for other redox-active drugs is highly likely as several other compounds such as Mn salens, nitroxides, and polyphenols also inhibit NF- κ B.

Studies as such have challenged how small molecule redox-active SOD mimics, originally considered as selective antioxidants, are viewed. Current data point to the activation of Nrf2 by different redox-active drugs including curcumin, sulforaphane, nitroxides, and Mn porphyrins, presumably via oxidation (or *S*-glutathionylation) of the cysteines of its Keap1 unit, reminiscent of the NF- κ B story described above. Such action would result in upregulation of endogenous antioxidative defenses. The data provided by Thambi Dorai et al. [14] on rat kidney ischemia/reperfusion injury showed that Mn porphyrin, rather than acting as SOD mimic in its own right, may activate Nrf2. Activation of Nrf2 would upregulate numerous endogenous antioxidative defenses including mitochondrial and extracellular SOD enzymes. Recent preliminary data from Daret St. Clair's group suggest that the activation of Nrf2 by Mn porphyrin may, though, not occur in cancer. Indeed the activation of Nrf2 by Mn porphyrin was not seen with malignant hematopoietic stem cells derived from patients with myelodysplastic syndrome, but Nrf2 was activated in normal hematopoietic stem cells.

In addition to favorable redox properties, redox-active therapeutics MUST reach a site of action in the body without imposing significant toxicity. Significant efforts have been invested towards understanding how structural properties of Mn porphyrins affect their toxicity and biodistribution in organs, cells, and subcellular organelles. Similar studies on other redox-active drugs are needed.

This book provides a comprehensive, up-to-date source of information on the molecular design and mechanistic, pharmacological, and medicinal aspects of redox-active therapeutics. The first two sections of the book discuss the role of SOD enzymes under physiological and pathological conditions and address multiple classes of redox-active drugs. The basic aspects of the chemistry and biology of redox-active drugs and the brief overview of the redox-based pathways involved in cancer and the medical aspects of redox-active drugs are provided assuming little in the way of prior knowledge. The third and fourth sections of the book deal with the therapeutic approaches towards different diseases. Among therapeutic effects obtained with redox-active drugs, the radioprotection of normal tissues is of particular interest as there is no efficacious and nontoxic radioprotector of normal tissue available for human use. Such effects gave rise to ongoing clinical trials on the radioprotective effects of two efficacious SOD mimics (Mn porphyrin-based BMX-001 and Mn cyclic polyamine-based GC4419)—a critical step forward in the development of a redox-active SOD mimic as a human therapeutic. Up to 50 % of all cancer patients undergo some type of radiotherapy; thus there is a substantial need to protect normal tissue during tumor irradiation. While protecting normal tissue, it is essential that the radioprotector does not protect tumor tissue. Multiple studies now show that an SOD mimic can simultaneously function as a radioprotectant for normal tissue and as a radiosensitizer for tumor tissue. Only recently has a possible explanation for such apparent dichotomy emerged. It relies on differential redox

environments of normal vs. cancer tissue and differential accumulation of Mn porphyrin in those tissues. This drives vast suppression of antiapoptotic NF- κ B in the cancer cell while there is only moderate suppression in normal cells; in turn, tumor cells undergo apoptosis while survival pathways are upregulated in normal cell.

In recent years there has been a rapid advance in developing and exploiting redox-active therapeutics towards a wide range of diseases and pathophysiological states other than cancer, such as inflammation, diabetes, cardiovascular, and neurodegenerative diseases. Contrary to classical therapeutic approaches that target directly specific proteins, enzymes, or macromolecules, redox-active therapeutics constitute a novel strategy whose target is the organism redox network, the so-called *Redoxome*. Mimics of redox enzymes and compounds that are able to reestablish the physiological levels of reactive species in normal tissues (demonstrated as a suppression of oxidative stress-dependent immune responses and secondary inflammatory processes), or selectively increase the oxidative burden in some targeted cells and tissues (such as tumor), are being heavily sought as experimental therapeutics. The adventure into fully understanding the effects obtained with metal-based therapeutics in inducing subtle changes, which would be observed as the “healing” of a diseased or death of a cancerous tissue, is still in its infancy; yet remarkable therapeutic effects are driving research in this relatively new interdisciplinary area linking chemistry, biochemistry, biology, and medicine.

The abundance of new information and the paradigm shift in our understanding of the mechanism of how the redox-active drugs work in a wide variety of diseases impose a need for a book to synthesize the current state of knowledge regarding the role of redox-active compounds in healthy and diseased tissue. Thus, this appears to be the first book fully dedicated to addressing the critical role that redox processes play in the development of different classes of therapeutics from the bench to the clinic and stressing awareness of these concepts for the treatment of disease. The chapters in this book describe the progresses in defining the central role of redox biology in many disease processes including inflammation, immunology, and neoplasia. This sets the foundation for the development of new classes of small redox-active molecules with unique effects in control of redox biology through modulation of key transcription factors at the core of inflammation, immunity, and neoplasia. The next decade shows a promise for the translation of this body of knowledge into new, transformative human therapeutics.

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7 years. With his dedication, passion for science, and hard work, Artak has made a tremendous impact on the development of redox-active therapeutics and understanding of their mechanism(s) of action(s). While organic chemist by basic training, he excelled also in in vitro and in vivo experiments in support of our aqueous chemistry. With his exquisite artistic skills, the brilliant figures in bright colors became a growing part of our manuscripts.

I am also grateful to numerous colleagues who helped us on our way toward clinical trials, many of whom coauthored chapters in this book. We are most obliged to Irwin Fridovich (Duke University School of Medicine); Peter Hambright (Howard University); Ludmil Benov (Kuwait University School of Medicine); Kam Leong (Duke University School of Engineering, presently at Columbia University); Daret St. Clair (University of Kentucky at Lexington); Margaret Tome (University of Arizona at Tucson); Jon Piganelli (University of Pittsburgh School of Medicine); Christopher Lascola, Darell Bigner, Mark Cline, Huaxin Sheng, Bridget Koontz, and David Warner (Duke University School of Medicine); Željko Vujašković (University of Maryland School of Medicine, Baltimore); John Archambeau (Loma Linda University); and Ting-Ting Huang (Stanford University School of Medicine and Geriatric Research Education and Clinical Center, Veterans Affairs Palo Alto Health Care System). Shortly after I joined Irwin Fridovich's Lab, I was fortunate to get acquainted with Peter Hambright. While Irwin Fridovich is the father of *free radicals in biology and medicine*, Peter Hambright may be regarded as the father of *water-soluble porphyrins*. I could not have imagined my career in water-soluble porphyrins, whose structural modifications resulted in powerful SOD mimics and redox-active therapeutics, without the inputs of Peter Hambright. In 1995, when I joined Irwin Fridovich's Lab, I essentially knew nothing about superoxide and porphyrins. While Irwin Fridovich taught me the basics of free radical biology and medicine, Peter Hambright, a fascinating character in his own right, was the one who guided me through my first steps in porphyrin chemistry. Unfortunately he passed away 5 years afterwards. Ludmil Benov has been in charge of all experiments related to the bioavailability of different redox-active drugs in simple unicellular models of oxidative stress, *Escherichia coli* and *Saccharomyces cerevisiae*. Most recently his studies on cancer and normal mammalian cells helped in identifying the best Mn porphyrin candidates for clinical development. Also, Benov's experiments increased our insight into the bioavailability of Mn porphyrins and mechanisms of their in vitro and in vivo actions. Margaret Tome, a biochemist whose experiments are nothing short of art, contributed vastly to understanding the in vivo pro-oxidative mechanism of action of Mn porphyrins. Kam Leong occupies a very special place in my career, a role model of a scholar and mentor and a man of immense kindness and generosity, who, while on faculty at Duke University School of Engineering, supported my Lab with his own funds in times of great need. With Bridget Koontz, we recently launched our journey toward radioprotection of male sexuality during radiotherapy of prostate cancer patients. With Željko Vujašković, we performed the very first mice studies on the pulmonary radioprotective effects of Mn porphyrins at Duke University, which were followed by monkey studies in collaboration with

Mark Cline (Wake Forest School of Medicine). Christopher Lascola pioneered the use of Mn porphyrins for differential tumor vs. normal tissue MR imaging. Darell Bigner (co-leader of The Preston Robert Tisch Brain Tumor Center at Duke) was instrumental in supporting the initial mouse studies on the anticancer therapeutic potential of MnTnBuOE-2-PyP⁵⁺ in glioma, facilitating its progress toward clinical trials as a radioprotector of normal brain while radiosensitizer of brain tumor. David Warner and Huaxin Sheng were the first to point out the therapeutic potential of Mn porphyrins in central nervous system injuries. The unsurpassable expert surgical skills and the compassionate nature of Huaxin Sheng have been invaluable with CNS injuries and pharmacokinetic studies. Daret St. Clair pioneered the role of Mn porphyrins in mitochondrial actions thereby mimicking MnSOD; in collaboration with her, we showed that cationic Mn porphyrins favor mitochondrial over cytosolic accumulation. Our over-decade-long joint work has developed into gentle and highly supportive friendship. Jon Piganelli, spirited, enthusiastic, and a very dear colleague of mine, has always trusted the therapeutic potential of Mn porphyrins. He was the first to suggest they act at the level of NF- κ B cysteines, supposedly as pro-oxidants challenging our views on Mn porphyrins as antioxidants. While provocative in the early 2000s, viewing the actions of so-called SOD mimics as pro-oxidative has been increasingly accepted by researchers nowadays. Importantly, Jon Piganelli was instrumental in getting MnTE-2-PyP⁵⁺ into clinical trials on islet transplants in Canada. A fine clinician, scientist, and a colleague, John Archambeau performed critical studies on proton radiation of rat rectum indicating the potential of Mn porphyrins as radioprotectants of the rectum and setting the stage for their development toward the clinic; related studies are in progress at Duke University. Christian Beausejour and Ting-Ting Huang conducted critical studies showing the therapeutic potential of Mn porphyrin in protecting hippocampal neurogenesis during irradiation, and substantiated similar studies conducted by Mark Dewhirst at Duke University. In collaboration with my Lab, Paula Lam, Emily Roberts/Xiaodong Ye/Kam Leong, Ludmil Benov and Margaret Tome showed that Mn porphyrins when combined with sources of reactive species (such as radio- and chemotherapy and ascorbate) induce differential effects in restoring the physiological environment of normal cells while killing cancer cells. We have just launched studies with Angeles Secord and Shara Reihani (Duke University School of Medicine) on the use of Mn porphyrins as single agents or combined with chemotherapy, radiotherapy, and ascorbate in ovarian and cervical cancer. The collaborations with Stephen Weber, University of Pittsburgh, and Robert Levy and Giovanni Ferrari, University of Pennsylvania School of Medicine, have just had an excellent start. An important place in addressing the therapeutic and mechanistic aspects of Mn porphyrins is occupied by the Uruguay group at Universidad de la República led by Rafael Radi and Gerardo Ferrer-Sueta; many of their students and colleagues have been involved in studies on Mn porphyrins during almost 20 years of collaboration, such as Homero Rubbo, Andres Trostchansky, and Madia Trujillo; they addressed peroxynitrite-related aspects of Mn porphyrins and are in a process of showing that Mn porphyrins also reduce hypochlorite. All of those studies paved the way toward clinical trials.

A special place in the development of electron-deficient metalloporphyrins occupies the information made available by Gordon M. Miskelly's group in *Richards et al., Inorg Chem* 1996 (vol 35, 1940–1944). The manuscript described the complex of Li with octabrominated *para N*-methylpyridylporphyrin. The enclosed pK_a values of the inner pyrrolic nitrogens indicated the exceptional acidity of the porphyrin, suggesting in turn the exceptional electron-withdrawing power of eight pyrrolic bromines. This report guided us towards the synthesis of the first powerful SOD mimic, MnBr₈TM-4-PyP⁺. That compound was unfortunately of insufficient metal/ligand stability (*Batinić-Haberle et al., Arch Biochem Biophys* 1997). In addition, the information from that manuscript helped us with isolation and purification of different Mn porphyrins.

Many other researchers in the USA and abroad contributed also to the development of Mn porphyrins such as Dean Jones and Judith Fridovich (Emory University); Joan Valentine and Edith Gralla (University of California at Los Angeles); Lee-Ann MacMillan-Crow and John Crow (University of Arkansas for Medical Sciences at Little Rock); Daniela Salvemini (St. Louis University School of Medicine); Jeannette Vasquez-Vivar (University of Wisconsin); Bruce Freeman (University of Pittsburgh Medical Center); Thambi Dorai (New York Medical College); Sidhartha Tan (University of Chicago); Rebecca Oberley-Deegan (University of Nebraska Medical Center); Christian Beausejour (University of Montreal); Fabio Doctorovich (University of Buenos Aires); Candace Floyd (University of Alabama at Birmingham); Paula Lam (Duke-National University of Singapore Graduate Medical School, Singapore); Daohong Zhou (Winthrop P. Rockefeller Cancer Institute, University of Arkansas for Medical Sciences); Miloš Filipović, Jan Miljković, and Ivana Ivanović-Burmazović (Friedrich-Alexander University, Erlangen-Nürnberg, Germany); Won Park (Sungkyunkwan University School of Medicine, South Korea); Nuno Oliveira and Ana Fernandes (Faculty of Pharmacy, Universidade de Lisboa and Universidade Lusófona, Portugal); João Laranjinha (Universidade de Coimbra, Portugal); Peter Humphries (Trinity College of Dublin, Ireland); Ana Budimir and Mladen Biruš (University of Zagreb, School of Pharmacy and Biochemistry, Croatia); Dragica Bobinac (University of Rijeka School of Medicine, Croatia); and Mutay Aslan (Akdeniz University Medical School, Antalya, Turkey).

Upon return from my Lab to the Universidade Federal da Paraíba, at João Pessoa, Brazil, Júlio S. Rebouças has established collaborations with his computational colleagues (Silmar do Monte, Elizete Ventura and Otávio de Santana) who have since addressed different aspects of the development of Mn porphyrins. We are enjoying the spirit and enthusiasm with which many students at Universidade Federal da Paraíba, though with limited resources, are conducting porphyrin research. While relishing the tropical paradise of the Brazilian Atlantic coast during the 5th SILQCOM Latin American Symposium on *Coordination and Organometallic Chemistry* hosted by Eduardo N. dos Santos, I had the opportunity to meet many other passionate scientists in Brazil working on different aspects of drug development, some of whom coauthored chapters in this book. Insightful chatting with Henry Forman has been always greatly appreciated. The work on chapter "SOD Mimetics and Related Redox-Active Molecules" in the fifth edition of the *Free*

Radicals in Biology and Medicine book gave us the opportunity to offer our modest contribution to the epic efforts of Barry Halliwell and John Gutteridge to make such encyclopedia-style book an essential reading for all of us.

The story on SOD mimics started in the late 1970s with the seminal discovery of Irwin Fridovich and Joe McCord of the function of copper protein as superoxide dismutase enzyme. The very first steps toward commercialization were implemented by James Crapo. We are indebted to James Crapo (CEO, BioMimetix JVLLC), Mark Dewhirst, Katy Peters and David Brizel (Duke University School of Medicine) for invaluable efforts in enabling the Mn porphyrin lead candidate, BMX-001, to enter the two clinical trials at Duke University and University of Colorado. I am also much obliged to James Crapo, for continuous support of my and Ivan Spasojević's Labs. We have been very fortunate for having our administrator Dianne Young around; her smiling face has been there when different issues needed immediate attention; she exceeded her work duties in making the working environment cheerful and comforting, especially at stressful times of shortage in funding. The kind support and encouragement of Christopher Willett, the chair of the Department of Radiation Oncology, Duke University School of Medicine, has been always greatly appreciated.

I am also grateful to those supervisors of mine whose patience, kindness, and generosity were critical in early steps of my career: Blaženka Sebečić, Dubravka Barišin-Kahlina, Ranko Babić, and Mladen Biruš. The invaluable support of Ivan Spasojević in my career and life has always been more than collaborative: his ingenuity and creativity made everything happen smoothly. Together we went through numerous scientific ups and downs; not only did Ivan contribute his technical expertise to our joint research efforts, but his wonderful sense of humor made our work fun. We started our research endeavors with inorganic magnesium-containing mixtures in the early and mid 1980s and continued with iron and vanadium chemistry and biology in the late 1980s. By good fortune, Alvin Crumbliss, then the chair of the Department of Chemistry, Duke University, had an opening to work on an NSF project; in times of civil war in my country, Yugoslavia, such an opportunity was nothing short of a miracle. Two and a half years of my and Ivan's joint work on host-guest recognition chemistry of iron siderophores and crown ethers resulted in eight manuscripts, out of which one was published in *JACS*. In January 1995, we embarked on over a 2-decade long SOD epic journey, eventually succeeding in our major goal—seeing our compounds reach first-in-human clinical trial in 2016. Our son, Siniša Haberle, who joined our research while at Duke University as a radiology resident, has been our lifelong inspiration and joy; his newborn son, Luka, will continue to be a source of immense happiness beautifying the routine of our days. Last, but not the least, the free and adventurous spirit of my mother, Paula Sertić-Batinić, had nourished my curiosity. Supported by enormous kindness and generosity of my father, Branko Batinić, she directed me through my early childhood toward passionately exploring the knowledge and the world pushing me toward learning several languages that “would open my doors to the world” as if knowing where I would eventually find my place on this beautiful planet Earth.

Ines Batinić-Haberle

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