Preface

The recent developments on understanding the challenging topic of nitric oxide (NO) and its derivatives in the field of cancer have yielded significant advances in the potential therapeutic use of NO-related donors in the fight against cancer, used either alone or in combination with other therapies to achieve synergy. The first book in this field "Nitric Oxide and Cancer: Prognosis, Prevention, and Therapy" was published in 2010 by Springer, New York. This book consisted of many reviews by authoritative scientists/ clinicians and included topics as follows: (1) The role of NO in the pathogenesis of cancer (2) The dual roles of NO in protecting or inducing cell death (3) The role of NO in metastasis (4) The chemo-immunosensitizing activities of NO (5) The prognostic significance of NO and (6) The therapeutic applications of NO. Hence, this first book provided a general introduction regarding the important role NO may play in cancer, a taboo subject that has not seriously been considered in the past.

This new book "Nitric Oxide and Cancer: Pathogenesis and Therapy" extends and adds several relevant advances that have been made in the last several years with a thorough understanding of the current status of NO in cancer and its potential therapeutic translational application in the clinic. This book has assembled contributions from experts in this field and reports on up to date reviews on novel findings on various topics of interest to both the scientific and non-scientific communities.

Part I deals with the "*Molecular cell signaling by NO in cancer*." Five contributions cover this topic. Doctors Du and Geller (University of Pittsburgh) reviewed the Wnt/β-catenin signaling pathways modulated iNOS/NO signaling in inflammation-induced carcinogenesis. They used transgenic animal models for their studies. Signals by iNOS/NO result in loss of heterozygosity of adenomatous polyposis colon (APC) and activate the Wnt/β-catenin signaling pathway and contribute to the development of cancer. In fact, inhibition of iNOS decreases the Wnt/β-catenin signaling and cancer growth. These investigators established three pathways for the interaction between iNOS and the Wnt signaling, namely (i) a positive feedback loop in which iNOS causes APC and β-catenin mutations and by Wnt-inducing iNOS expression (ii) a negative feedback between Wnt and Dichhoff-1 (DKK1) in which iNOS inhibits DKK1 gene expression and (iii) cross-regulation between the NF-κB and Wnt/β-catenin pathways through iNOS/NO genes. They suggested

that combining iNOS inhibitors with NSAIDs may synergize for more potent anti-cancer effects. Dr. Yakovlev (Virginia Commonwealth University) reviews "*Nitric Oxide and Genomic Stability*." It is well established that inflammation induces iNOS and results in the overproduction of NO and reactive nitrogen species (RNS) that participate in carcinogenesis by different mechanisms. Dr. Yakovlev discusses the NO/ RNS-dependent mechanisms of genomic instability and bystander effects. He reviews the mechanisms of "*Synthetic lethality*" of NO-RNS donor/PARP inhibitor combination in sensitizing cancer cells to DNA-mediated damage effects. Dr. Scicinski and colleagues (Mountainview, California) review "*Targeting hyponitroxia in cancer therapy.*" Hyponitroxia is a pro-neoplastic effector and they review strategies to reverse this effect by increasing NO and killing the tumor cells. NOS is inhibited due to hypoxia and stimulation under oxic conditions. They discuss attempts to manipulate hypoxia in cancer treatments and they postulate that manipulation of NO levels may represent a potential conversion form hypoxia to enoxia as a function of mutually reinforcing the relationship of NO and oxygen. Dr. Glynn and colleagues (National University, Ireland) discussed "*The role of NO in tumor invasion and metastasis*." They proposed that NOS expression in tumor epithelia has a tumor promoting activity, while NOS expression in tumor-associated macrophages has an anti-tumor activity. Hence, tumor progression/ regression depends on the balance between these two NO-associated activities. They present a challenging complexity of the cellular source of NO, the direct exposure and the amount of NO, all of which, form NO-mediated suppressive or stimulating activities in the tumor microenvironment. They proposed that more research is warranted to achieve a highly selective application to favor anti-tumor activity over pro-tumor activity by NO. Dr. Postovit (University of Alberta) reviews "*The role of NO in the regulation of the pro-tumorigenic and hypoxic phenotype.*" Clearly, tumor hypoxia correlates with poor clinical prognosis. Dr. Postovit discusses how NO can mimic and mitigate the effect of hypoxia in tumors as a function of the NO concentration. Several clinical trials have been used as examples in which NO-mediated anti-tumor effects correlated with inhibition of hypoxia. Furthermore, a report is discussed in which patients were treated with GTN and resulting in an increased response rate and decreased time to progression in stages IIIb/IV NSCLC treated with cis platinum and vinorelbine. Further, a retrospective study showed that GTN increases the response rate of patients with lung cancer treated with docetaxel and carboplatin. The patients treated with GTN showed decreased levels of VEGF and HIF-1α, corroborating the role of NO in mitigating the pro-tumorigenic effects of hypoxia. Dr. Postovit cautions of NO-mediated treatments to consider the paradoxical role of NO in the regulation of hypoxia-induced manifestations.

Part II covers three reviews on "S-nitrosylation and cancer." Dr. Brown and colleagues (Columbia State University) discussed "The signaling mediated by NO and through its S-nitrosylation of various proteins and their impact on the tumor cells." S-nitrosylation is reversible and involves the attachment of a nitroso moiety to the reactive thiol/cysteine residues and producing S-nitrothiol (SNO). Several proteins have been reported to be S-nitrosylated that are involved in transcription, DNA repair, and apoptosis, and also proteins involved in tumorigenesis. These investigators

have summarized in a table format several proteins that are S-nitrosylated and that are involved in either the progression or inhibition of cancer. Clearly, a better understanding of the mechanisms of signaling and consequences of S-nitrosylation is needed to enable the selective anti-tumorigenic activity over the pro-tumorigenic activity. Dr. Jeannin and colleagues (Burgundy University, Dijon, France) review "S-nitrosylation of cancer cells." They discussed several protein targets of chemotherapy that are S-nitrosylated. They discuss the potential role of activation of death receptor signaling pathways by NO to treat tumors. They elaborated on the role of NO in the regulation of death receptors, directly or indirectly, and how in combination with chemotherapeutics result in synergistic anti-tumor effects. Clearly, the potential clinical application of suitable NO donors in combination with chemotherapeutic drugs may result in an improved clinical response in cancer patients. Doctors Luanpitpong and Rojanasakul (West Virginia University) discussed "The role of S-nitrosylation in cancer metastasis." They reviewed the roles of S-nitrosylation in cancer focusing on anoikis, resistance, cell invasion, migration, and angiogenesis, all of which are key events in metastasis. In their review, they discuss the role of the constitutively activated PI3K-AKT signaling pathway, in turned on or off, via S-nitrosylation of the phosphatase PTEN. PTEN activity is inhibited by S-nitrosylation and, thus, enhances PI3K-AKT activity and cell survival. The mechanism of anoikis resistance in cancer and S-nitrosylation were well discussed. In addition, they also discuss the S-nitrosylation of various proteins involved in metastasis and apoptosis, including FLIP, Bcl2, cavolin 1, c-Src, EGFR, Ras, MMP-9, etc. These various S-nitrosylated proteins are shown to play an important role in the metastatic cascade and resistance to apoptosis.

Part III deals with the "*Modulation of anti-tumor immune responses by NO*." Three contributions are presented. Dr. Garban (University of California, Los Angeles) reviews "*The role of NO on the anti-tumor immune response*." He discusses the reported literature on the role of NO in the sensitization of drug-resistant tumor cells to immune-mediated cytotoxic activities. In addition, he discusses the role of NO-mediated modification of proteins that results in the potentiation of antigenicity. For instance, he refers on the role of NO in IL-2-mediated activation of anti-tumor response. He summarizes the role of NO on the inhibition of the constitutively activated NF-κB pathway and downstream inhibition of anti-apoptotic gene products as well as pro-inflammatory cytokines. In addition, he discusses the role of NO on the inhibition of the resistant factor Yin-Yang 1 (YY1) and FOXP3. Dr. Siesjo (Lund University, Sweden) reviews "*The regulation of anti-tumor immune response by NO.*" He discusses the contrasting roles of NO by direct cytotoxicity and by inhibition of anti-tumor immune reactivity. He elaborates on the role of NO on the regulation of both central and peripheral tolerance. Among the topics discussed, he reviews the regulation of T-cells activated by NO, the immune-suppressive role of NO, the potentiation of anti-tumor cytotoxic cells by NO, the role of dendritic cells and suppressor cells modulated by NO and the mechanism of NO-mediated immune suppression. He attributes the obstacle in manipulating NO in cancer therapy due to the lack of clinically approved NO donors or NO inhibitors. He also suggests the potential of combination of immunotherapy and NO-modulating agents

on the fight against cancer. Dr. Doctors Janakiram and Rao reviewed "*Nitric Oxide: Immune modulation of tumor growth*." It is well known that in the tumor microenvironment NO is generated by tumor cells, infiltrated cells, and tissue cells in the microenvironment. Hence, the generation of NO and its levels play a pivotal role in the regulation of tumor growth, both as an enhancer and as a repressor. Clearly, this complexity of the tumor microenvironment and the interaction of tumor cells with the infiltrating immune cells create a system that is not predictable and thus, difficult to establish the best approach to favor NO anti-cancer effects through the use of NO donors or NO inhibitors in clinical therapy.

Part IV deals with "*Therapeutics and overcoming resistance.*" Dr. Bonavida reviews the "*Role of NO in chemo-immune resistance*." In this review, he focused on the underlying mechanisms that regulate resistance and how NO treatment results in the reversal of resistance. Emphasis was placed on a dysregulated loop in cancer cells, namely, the NF-κB/Snail/YY1/RKIP loop, that was reported to regulate both drug and immune resistance. Each gene product in the loop was reported to regulate resistance as assessed by the use of specific inhibitors. Treatment with NO donors leads to the modification of the dysregulated loop resulting in the inhibition of NF-κB, Snail, and YY1 and concomitantly with the derepression and the upregulation of RKIP. The mechanism of inhibition of NO was examined and was found to be, in part, due to the direct S-nitrosylation of NF-κB (p50 and p65) and also by S-nitrosylation of Snail and YY1. The direct inhibition of NO as well as indirect inhibition of YY1 and Snail through NF-κB inhibition resulted in upregulation of RKIP and reversal of resistance. In addition, evidence was presented on the activity of NO donors in chemo-immunosensitization of resistant cells. A discussion was provided on the role of NO on inhibiting EMT via inhibition of the loop since inhibition of Snail, a metastasis inducer, was responsible, in part, to the inhibition of EMT and metastasis. Dr. McCarthy and McCrudder (University of Belfast, UK) discuss "*Emerging role of NO-mediated therapeutics*." They reviewed the emerging strategies of utilizing NO-mediated therapeutics for cancer. They also review the role of iNOS gene therapy and its limitations, which was not effective *in vivo*. These investigators have reported a novel inducible and tumor-specific activation of the *iNOS* gene for therapy. Using inducible promoters, they were able to deliver the *iNOS* gene for therapy and observed a delay in tumor growth. They pointed out that, in combination, treatments with high concentrations of NO may not result in antitumor activity. For example, NO can react with some chemo-therapeutic drugs such as etoposide and abolishes its activity. Other examples of iNOS upregulation for promoting tumor growth were presented. Doctors Rapozzi and Della Pietro (University of Udine, Italy) reviewed "*The role of NO in photodynamic therapy (PDT).*" PDT is clinically used therapeutically for treatment of early stages of cutaneous tumors. As PDT may induce apoptotic effects, these investigators have examined the role of NO in mediating PDT anti-tumor response. They discussed the induction of iNOS/NO by PDT and NO-mediated tumor cell death by PDT. They also discussed the alternatives to delivering NO-releasing compounds to enhance PDT anti-tumor response. They present the possibility of conjugating NO with a photosensitizer in PDT. This is a new application of PDT which has significant clinical ramifications.

Dr. Muntane and colleagues (University of Sevilla, Spain) reviewed "*The inhibition of cell death signaling by NO in cancer cells*." They discuss the role of NO in anti-tumor activity by the regulation of stress response mediated by HIF1-α and p53 that lead to cell growth arrest and apoptosis. They also discuss the induction of DNA damage by NO, the increase of p53 and cell death. They report that NO nitrosylates critical thiols in DNA repair enzymes in hepatoma cells that results in chemo-sensitization. Dr. Scicinski and colleagues (Mountainview, California) review "*Discovery and development of RRX-001*." They have developed a new compound, RRx-001, the first of a class of NO-mediated epigenetic anti-cancer agents. They reported that RRx-001 (designed by combining two structural components, a di-nitroazetidine derived from TNAZ [tri-nitroazetidine] and α-bromoacetate) was active as a single agent *in vitro* and *in vivo* against tumor cell lines. They describe the mechanisms by which RRx-001 mediates its activity via NO. They have completed a phase I study with RRx-001 and, aside from phase I end point, they also found clinical benefits in 70% of patients with multiple tumor types. Of interest, RRx-001 sensitized patients who previously failed therapy. Based on these positive findings, a phase II is being considered.

Part V deals with "*NO-mediated alterations in gene products*." Dr. Othman and colleagues (Northwestern University) review "*The role of NO in coagulation in cancer*." It is well known that NO is a rapid vasodilator and inhibitor of coagulation. Cancer patients are at high risk of developing venous and arterial thrombo-embolic events. They discuss the relationship of pro-coagulant factors and NO, the role of NO and global hemostasis, the link among hypoxia, NO, and coagulation, NO as a fibrinogen system, and NO and thrombosis. They also discuss both the pro and anti-tumorigenic effects of NO-mediated therapies. Doctors Mutus and Sin (University of Windsor, Canada) review "*The relationship between neutral sphingomyelase 2 and NO and their implications in cancer therapy*." Neutral sphingomyenase 2 is a regulator of ceramide and sphingolipid signals. Under oxidative stress, such as anti-cancer drugs, the level of SMase2 is upregulated resulting in increased levels of cellular ceramide, which lead to activate pathways that lead to apoptosis.

Clearly, the above contributions have added a new dimension in understanding the complex roles of NO in cancer and have presented several mechanisms of its multiple effects and its potential for therapy when used under optimal conditions. It is, noteworthy, that current studies are aimed at developing novel NO donors that will be effective in the treatment of highly resistant cancer as well as preventing metastasis, when used alone or in combination with sub-toxic therapeutics. In addition, current studies are also exploring the development of complexes consisting of NO and other agents for targeted delivery to enhance specificity and reduce toxicity.

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http://www.springer.com/978-3-319-13610-3

Nitric Oxide and Cancer: Pathogenesis and Therapy
Bonavida, B. (Ed.)
2015, XXIII, 308 p. 46 illus., 33 illus. in color., Hardcover
ISBN: 978-3-319-13610-3