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The Role of PDE-5 Inhibitors in Prostate Cancer

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1. Introduction

Prostate cancer currently stands as the most frequently diagnosed solid tumor in men, and remains one of the leading causes of cancer mortality in men in the Western world, accounting for an estimated 32,050 deaths in the United States in 2010 (Jemal *et al.*, 2010). With the well-known use of serum prostate-specific antigen (PSA) as a screening tool, men are being diagnosed with earlier stage disease at younger ages. However, a significant number of men continue to be diagnosed with high-risk localized prostate cancer. Radical prostatectomy, radiotherapy, cryotherapy, high-intensity focused ultrasound, radiation therapy, and androgen deprivation as well as androgen receptor blockade have been the mainstays of treatment for cancer patients with localized and androgen-dependent prostate cancer.

As prostate cancer cell growth is androgen dependent, its deprivation is an important therapeutic strategy. However, long-term androgen-ablation results in androgen-independent cancer cell growth in metastatic patients, leading to hormone refractory prostate cancer (HRPC) (Sonpavde *et al.*, 2006). Prostate cancer tends to invade the pelvic lymph nodes and spread to distant organs, mainly via the blood stream, showing a strong predilection for bones (Koutsilieris, 1993;Sourla *et al.*, 1996). This disease frequently metastasizes to bone and almost invariably progresses from an androgen-sensitive to an androgen-independent status, greatly limiting therapeutic options and significantly reducing life expectancy in patients. Skeletal metastases occur in more than 80% of cases of advanced-stage prostate cancer and they confer a high level of morbidity. Metastasis of prostate cancer, like that of other solid tumors, involves multiple steps, including angiogenesis, local migration, invasion, intravasation, circulation and extravasation of tumor cells and then angiogenesis and colonization in the new site. Treatment-naive metastatic prostate cancer is largely sensitive to androgen-deprivation therapy (ADT), but the effectiveness of ADT is temporary, and tumors in the majority of patients eventually relapse and evolve into castration-resistant prostate cancer (CRPC), from which most patients die (Eisenberger and Walsh, 1999). These tumors eventually become incurable or resistant to antihormonal therapy. Indeed, there is an association between ADT and high risk of cardiovascular disease and mortality, and men with a history of recent or active cardiac disease are particularly at risk (Saigal *et al.*, 2007). In men with a history of coronary artery disease, chronic heart failure, or myocardial infarction, ADT was associated with an increased risk of mortality (Nguyen *et al.*, 2011). Continuous ADT use for at least 6 months in older men is also associated with an increased risk of diabetes and fragility fracture (Alibhai *et al.*, 2009). For this reason, new agents and therapeutic modalities are needed,

including non-hormonal systemic chemotherapy, which can provide another option for patients with non-localized HRPC or CRPC.

2.1 Chemotherapeutic agents

Chemotherapy is often used as a main regimen in the overall treatment of most cancers. In the past, clinical trial design has focused on sequential development of chemotherapeutic drugs based on symptoms and number of prior therapies. There are four chemotherapeutic agents that the US Federal Drug Administration (FDA) approved for CRPC: estramustine, mitoxantrone, docetaxel and cabaxitaxel.

2.2 Docetaxel

Chemotherapy, using Taxotere (docetaxel), a member of taxane family, remains the standard option for patients at the advanced stages, in particular, HRPC (Schurko and Oh, 2008). As of April 2010, only one approved chemotherapeutic agent, docetaxel, showed promising results in improving survival in patients with metastatic CRPC (Abdulla and Kapoor, 2011). This drug is a microtubule-polymerizing agent with a well-established antimitotic chemotherapy action. It causes downregulation of anti-apoptotic protein, Bcl-2 (Li *et al.*, 2005;Schiff and Horwitz, 1980;Schurko and Oh, 2008;Stein, 1999;Yoo *et al.*, 2008), enhances the apoptosis induced by "tumor necrosis factor-related apoptosis-inducing ligand" (TRAIL) (Yoo *et al.*, 2008), down regulates genes involved in cell cycle progression (cyclin A, cyclin F, *CDC2*, *CDK2*, *BTG*, etc.), transcription factors (transcription factor A, ATF5, TAF 1 31L, etc.), oncogenes (*GRO*, *BRCA1*, *p120*, etc.) and apoptosis as *GADD45A (Li et al., 2005;Stein, 1999;Yoo et al., 2008)*. A recent study showed that docetaxel upregulates p53 and p21 in a p38-dependent manner to desensitize prostate cancer cells (Gan *et al.*, 2011). The p38/p53/p21 signaling pathway could be important for regulating the susceptibility towards docetaxel in prostate cancer. Docetaxel regimens have been shown to increase survival compared to previous treatment modalities in HRPC, although prognosis remains poor and median survival ranges from 10 to 20 months (Petrylak *et al.*, 2004;Tannock *et al.*, 2004). Cancer cells become resistant to taxanes and other microtubule-binding chemotherapeutic agents and therefore docetaxel therapy is limited. Makarovskiy et al. found that continuity of docetaxel exposure induces the formation of resistant giant multinucleated clones (Makarovskiy *et al.*, 2002). Lack of curative treatments at the advanced prostate cancer, underline the importance of additional trials for the successful development of an effective therapeutic approach. Another study showed that docetaxel and sodium selenite combination plays an antiproliferative synergistic and additive cell death effect (Freitas *et al.*, 2011). That study suggested that docetaxel and sodium selenite combination may be more effective in prostate cancer treatment than docetaxel alone warranting further evaluation of this combination in prostate cancer therapeutic approach.

Docetaxel in combination with prednisone compared with mitoxantrone in combination with prednisone yielded an extension in median survival with HRPC, however, patients eventually developed progressive disease associated with poor outcomes (Berthold *et al.*, 2008). Carbazitaxel, a tubulin-binding semi-synthetic taxane, is the first drug to improve survival in patients with metastatic CRPC whose disease has progressed during or after docetaxel-based therapy, providing a 30% reduction in the risk of death and an improved median overall survival compared with mitoxantrone (de Bono *et al.*, 2010). Carbaxitaxel in combination with prednisone was approved by the FDA in June 2010 for the treatment of patients with metastatic CRPC who had been previously treated with docetaxel (Wu *et al.*, 2011).

Although there are several options after failing hormone therapy to help achieve disease control, HRPC remains incurable, and there continues to be an ongoing need for the development of new therapies that provide significant survival benefits without severely impacting quality of life. Today, not only are hormonal and cytotoxic treatment modalities available to patients with metastatic CRPC, but also more novel treatments in the areas of immune and targeted therapies are being offered. Newer agents currently being investigated for their potential role in metastatic CRPC are sipuleucel T (an autologous dendritic cell-based vaccine), denosumab (antibody), abiraterone (hormonal therapy), TAK-700 (hormonal therapy), MDV3100 (hormonal therapy) and ipilimumab (immune therapy), zibotentan (endothalin-receptor antagonists) and dasatinib (tyrosine kinase inhibitor).

2.3 Doxorubicin

Anthracyclines rank among the most important chemotherapeutic drugs with a large spectrum of antitumor activity, including prostate cancer. The precise mechanisms of action of anthracyclines in tumor cells remain a matter of controversy. The suggested mechanisms include (i) DNA intercalation, leading to inhibition of synthesis of macromolecules; (ii) generation of reactive oxygen species (ROS), leading to DNA damage or lipid peroxidation; (iii) DNA binding and alkylation; (iv) DNA cross-linking; (v) interference with DNA unwinding or DNA strand separation and helicase activity; (vi) direct membrane effects; (vii) initiation of DNA damage via inhibition of topoisomerase II; and (viii) induction of apoptosis in response to topoisomerase II inhibition (Takemura and Fujiwara, 2007). Doxorubicin (DOX, Adriamycin) and its analogue epirubicin, or 4-epidoxorubicin, are the most potent anthracyclines, and have a broad spectrum of activity against solid tumors and hematological malignancies. Monotherapy with DOX or in combination with other agents, have been used extensively for the treatment of HRPC, however, controversial results have been reported (Petrioli *et al.*, 2008). Acquisition of chemoresistance remains one of the major problems of chemotherapy failure in cancer patients. Therefore, there is an urgent need to identify a strategy that can overcome chemoresistance and sensitize tumor cells to chemotherapeutic agents. For this reason, a clinical chemotherapeutic regimen consisting of a combination of drugs can achieve a higher therapeutic efficacy than that provided by a single drug.

2.4 Cardiotoxicity

Despite its clinical efficacy, the use of DOX is associated with their severe toxicity, including a myelosuppression and dose-dependent delayed and progressive irreversible cardiomyopathy often observed several years after cessation of treatment eventually results in refractory cardiac dysfunction (Steinherz *et al.*, 1991;Steinherz *et al.*, 1995). It has been shown that DOX induces cardiomyopathy and heart failure in >30% patients receiving 500 mg/m^2 or higher cumulative doses (Menna *et al.*, 2011;Minotti *et al.*, 2004). The molecular basis for this cardiotoxic effect remains a matter of debate. Several hypotheses have been suggested to explain the acute and chronic cardiotoxicity of DOX; these include the increased level of ROS and lipid peroxidation by DOX-iron cmplexes (Myers, 1998), along with a reduction in the levels of antioxidants and sulfhydryl groups (Takemura and Fujiwara, 2007), alterations in cardiac muscle gene expression, sensitization of Ca^{2+} release from sarcoplasmic reticulum channels, mitochondrial DNA damage and dysfunction and alteration of membrane potentials, and induction of apoptosis (Arola *et al.*, 2000;Burke *et al.*, 2002;Kumar *et al.*, 2001;Olson and Mushlin, 1990). Of these options, the free radical and ROS hypothesis of DOX-induced cardiotoxicity has gained the most support in previous studies.

The target organelles of DOX toxicity in cardiomyocytes are mitochondria wherein DOX accumulates with time (Kalyanaraman *et al.*, 2002;Konorev *et al.*, 1999). DOX-induced cardiomyopathy occurs predominantly via the generation of ROS in the cardiomyocyte mitochondria, a mechanism that is separate from its antineoplastic activity, which occurs primarily through inhibition of topoisomerase II (Myers, 1998). DOX is known to generate free radicals either by redox cycling between a semiquinone form and a quinone form or by forming a DOX-Fe^{3+} complex (Davies and Doroshow, 1986). In both pathways, molecular oxygen is reduced to superoxide anion ($O_2^{-}\cdot$), which is converted to other forms of reactive oxygen species such as hydrogen peroxide (H_2O_2) and hydroxyl radical ($OH\cdot$). Mitochondrial enzymes (e.g. NADH dehydrogenase) activate DOX by converting it to the corresponding semiquinone which generates superoxide in the presence of molecular oxygen. The dismutation of the superoxide, spontaneous or catalyzed by superoxide dismutase (SOD) enzymes, generates hydrogen peroxide in mitochondria (Kalyanaraman *et al.*, 2002). The heart is particularly vulnerable to free radical injury because the drug causes the disappearance of cardiac glutathione peroxidase, leaving the heart with no means of disposing of the hydrogen peroxide (Myers, 1998). These free radicals could then cause membrane and macromolecule damage, both of which lead to injury to the heart, an organ that has a relatively low level of antioxidant enzymes such as SOD and catalase (Doroshow *et al.*, 1980). Several studies demonstrated that DOX-induced cardiotoxicity can be largely reduced by the overexpression of the antioxidant enzymes mitochondrial superoxide dismutase (MnSOD), metallothionein, or catalase (Kang *et al.*, 1996;Kang *et al.*, 1997;Yen *et al.*, 1996). Moreover, free radical scavengers including probucol, amifostine, and dexrazoxane have demonstrated protection from doxorubicin-induced cardiotoxicity, further substantiating the role of ROS in DOX-induced cardiotoxicity (Koning *et al.*, 1991;Kumar *et al.*, 2001;Nazeyrollas *et al.*, 1999). On the other hand, all of these agents have pronounced clinical disadvantages, including a significant decline in high-density lipoprotein (HDL) levels, an inability to prevent DOX-induced mortality and weight loss, and potentiation of myelosuppression (Liu *et al.*, 2002b).

DOX induce cardiotoxicity ultimately results in myocyte apoptosis which plays an important role in the development of heart failure (Hosseinzadeh *et al.*, 2011;Mizutani *et al.*, 2005;Spallarossa *et al.*, 2004;Spallarossa *et al.*, 2009). In fact, apoptosis contributes to cardiomyocyte loss, which eventually leads to structural changes maladaptive to normal cardiac physiological demands (Narula *et al.*, 1996;Singal *et al.*, 2000). Strategies for the prevention of DOX-induced cardiotoxicity during chemotherapy have focused on three main approaches: dose optimization, synthesis of analogues and combination therapy. However, none of the analogues available clinically appear to have any advantage over DOX (Weiss, 1992); a better anthracycline has yet to be found. Today, liposomal formulations of anthracyclines are available; treatments have lower toxicity profiles, especially in terms of cardiac side-effects (Safra, 2003). The activity of anthracyclines is therefore an area worthy of further research in this clinical setting.

3.1 PDE-5 inhibitors

Cyclic nucleotide phosphodiesterases (PDEs) are a family of related phosphohydrolases that selectively catalyze the hydrolysis of the 3′ cyclic phosphate bonds of cAMP and cGMP, second messengers in the cell (Bender and Beavo, 2006). The PDE enzymes, of at least 11 types, are ubiquitous through out the body, and perform a variety of functions (Kukreja *et al.*, 2004). PDE-5 is the primary enzyme in the corpus cavernosum, and plays a crucial role in vascular smooth muscle contraction through controlling the rate of hydrolyzation and subsequent

degradation of cGMP (Bender and Beavo, 2006). Three widely prescribed PDE-5 inhibitors, sildenafil (Viagra), vardenafil (Levitra), and tadalafil (Cialis), have proven very effective for the treatment of erectile dysfunction (ED) in men (Boolell *et al.*, 1996;Porst *et al.*, 2001;Porst *et al.*, 2003) and more recently for pulmonary artery hypertension (Galie *et al.*, 2005;Galie *et al.*, 2010). In the lung, inhibition of PDE-5 opposed smooth muscle vasoconstriction and attenuated the rise in pulmonary artery pressure and vascular remodeling (Sebkhi *et al.*, 2003).

Several studies have shown that PDE-5 inhibitors induce a preconditioning-like effect against ischemia/reperfusion (I/R) injury in the intact heart and adult cardiomyocytes (Bremer *et al.*, 2005;Das *et al.*, 2004;Das *et al.*, 2005;Das *et al.*, 2008;Das *et al.*, 2009;Ockaili *et al.*, 2002;Salloum *et al.*, 2003;Salloum *et al.*, 2007;Salloum *et al.*, 2008). The mechanisms of cardioprotection include nitric oxide (NO) generation by activation of eNOS/iNOS (endothelial nitric oxide synthase/inducible nitric oxide synthase), activation of protein kinase C, cGMP-dependent protein kinase (PKG) and ERK, and inactivation of GSK3β and opening of the mitoK$_{ATP}$ channels (Das *et al.*, 2004;Das *et al.*, 2005;Das *et al.*, 2008;Das *et al.*, 2009;Ockaili *et al.*, 2002;Salloum *et al.*, 2003). PDE-5 inhibition attenuated cardiomyocytes cell death resulting from necrosis and apoptosis after SI-RO (simulated ischemia and reoxygenation) by NOS-dependent up-regulation of the Bcl-2/Bax ratio (Das *et al.*, 2005). Sildenafil attenuated ischemic cardiomyopathy in mice by limiting necrosis and apoptosis and by preserving left ventricular (LV) function possibly through a NO-dependent pathway following myocardial infarction by left anterior descending coronary artery ligation (Salloum *et al.*, 2008). Tadalafil also limits myocardial I/R injury and dysfunction through hydrogen sulfide (H_2S) signaling in a PKG-dependent fashion (Salloum *et al.*, 2009).

3.2 PDE-5 inhibitors protect against DOX-induced cardiomyopathy

Sildenafil attenuated cardiomyocyte apoptosis and left ventricular (LV) dysfunction in a chronic model of DOX-induced cardiotoxicity (Fisher *et al.*, 2005). Treatment with clinically relevant doses of sildenafil (0.7 mg/kg IP) prior to DOX treatment inhibited cardiomyocyte apoptosis, preserved mitochondrial membrane potential (Δψm) and myofibrillar integrity, prevented of LV dysfunction as well as ST prolongation. Reduction in fractional shortening and abnormalities in the nonspecific T wave and ST segment of Electrocardiography (ECG) was typically observed in DOX-induced ventricular dysfunction (van Acker *et al.*, 1996). Our ECG study indicated the most marked increase in ST interval occurred between week 4 and week 8 of DOX treatment. Furthermore, ST interval of sildenafil and DOX groups remained unchanged from baseline during the course of the study. This study demonstrated that sildenafil significantly protected against ST-interval prolongation throughout the study period.

Exposure of adult mouse ventricular myocytes to DOX resulted in dissipation of Δψm as illustrated via JC-1 immunofluorescent staining (Figure 1C, G), which leaded to the induction of apoptosis (Figure 1H) compared to control (Figure 1A). In contrast, sildenafil pretreatment with DOX demonstrated preservation of the Δψm (Figure 1D, G) and reduction of apoptosis (Figure 1H). However, sildenafil-induced protection was abolished by N^G-nitro-L-arginine methyl ester (L-NAME, an inhibitor of NOS) and 5-hydroxydecanoate (5-HD, mitoK$_{ATP}$ channel blocker). These findings implied that sildenafil-mediated protection from DOX-induced cardiomyocyte apoptosis is NOS dependent and established a significant role of mitoK$_{ATP}$ channel opening in sildenafil-induced cardioprotection. Additionally, the anti-apoptotic protein Bcl-2 was significantly declined after treatment in the DOX group compared with the sildenafil + DOX and control groups, suggesting a pivotal role of Bcl-2 in altering the pathological process leading to end-stage heart failure.

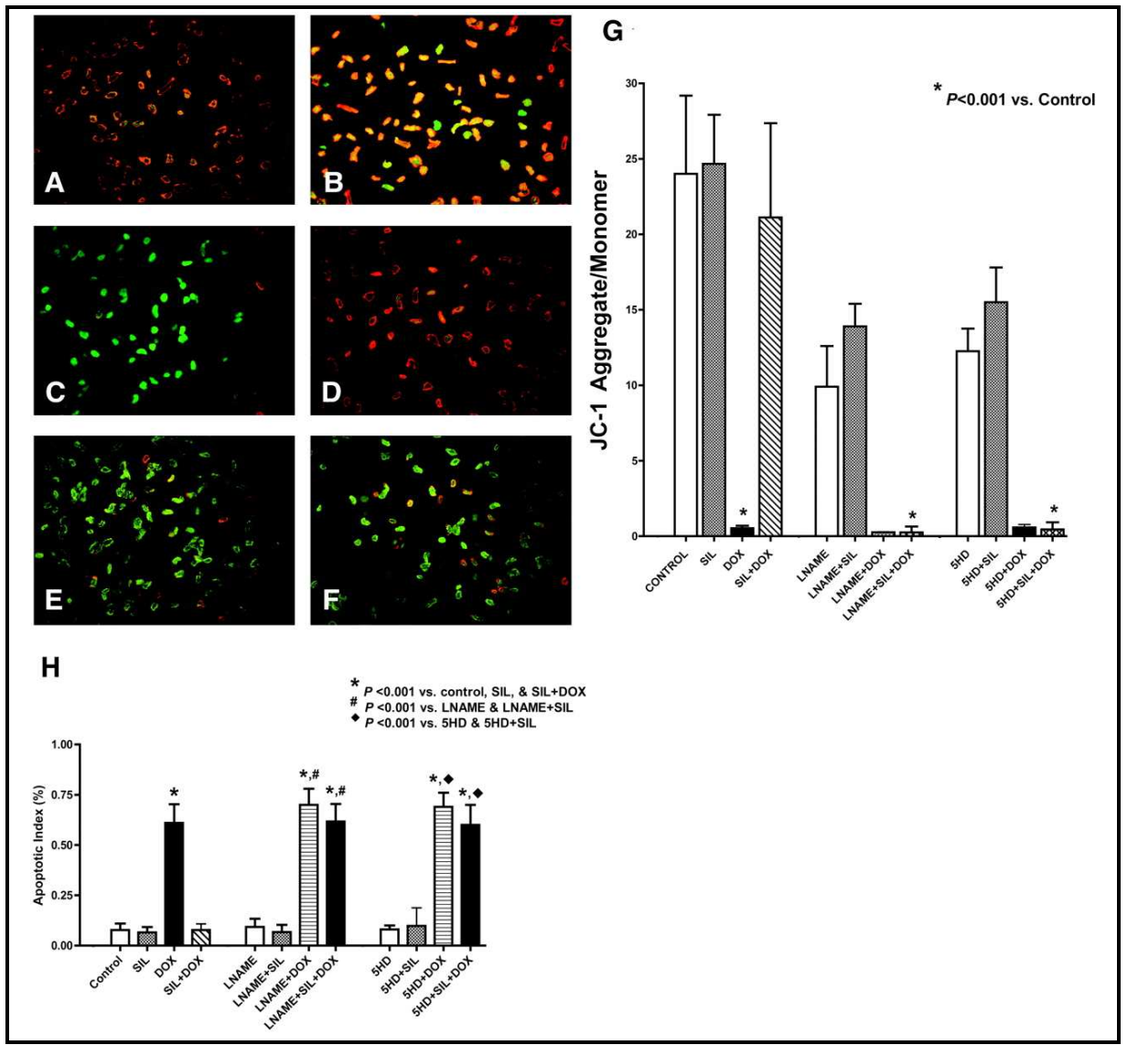

Fig. 1. Effect of sildenafil on Δψm and apoptosis in adult mouse ventricular myocyte. **A to F**, JC-1 staining of cardiomyocytes. Red fluorescence represents the mitochondrial aggregate, indicating intact mitochondrial membrane potential. Green fluorescence represents the monomeric form of JC-1, indicating dissipation of Δψm. **A**, Control; **B**, sildenafil (1 μmol/L); **C**, DOX (1 μmol/L); **D**, sildenafil (1 μmol/L) plus DOX (1 μmol/L); **E**, L-NAME (100 μmol/L)+sildenafil+DOX; **F**, 5-HD (100 μmol/L) +sildenafil+DOX; **G**, ratio of mitochondrial aggregates to monomeric form of JC-1; **H**, Apoptotic Index for TUNEL-positive cardiomyocytes. Data are mean±SEM (n=3; magnification X200). Reprinted from Fisher, P. W. et al. Circulation 2005;111:1601-1610 with permission.

More recently, we showed that tadalafil, the long acting PDE-5 inhibitor, also improved LV function by preserving fractional shortening (LVFS) and ejection fraction (LVEF) compared with DOX-treated mice (Figure 2) (Koka *et al.*, 2010). This study also demonstrated that tadalafil improved survival rates in mice without interfering with the anti-tumor effect of DOX. Tadalafil prevented cardiomyocyte apoptosis in DOX-induced cardiomyopathy through up-regulation of cGMP (Figure 3A) and PKG activity (Figure 3B), by restoring Bcl-2 and GATA-4 in the myocardium, and by reducing the oxidative stress via the up-regulation

of mitochondrial superoxide dismutase (MnSOD). Moreover, tadalafil did not interfere with the efficacy of DOX in killing human osteosarcoma cells *in vitro* or its antitumor effect *in vivo* in tumor xenograft model. These studies suggest that prophylactic treatment with the class of PDE-5 inhibitors might become a promising therapeutic intervention for managing the clinical concern of DOX-induced cardiotoxicity in patients.

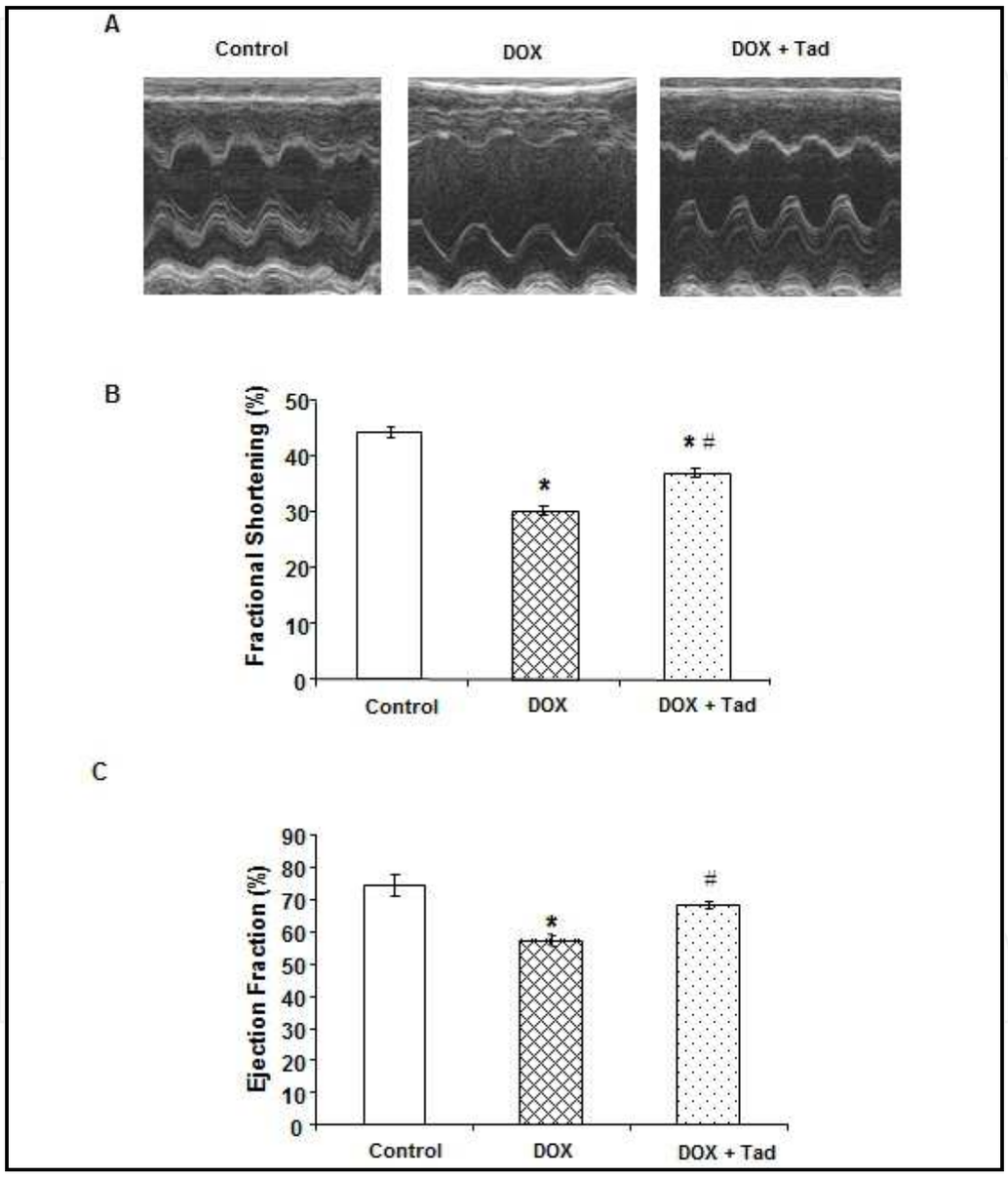

Fig. 2. Transthorasic echocardiography represented the effect of tadalafil on ventricular contractile dysfunction caused by DOX. **A,** representative M-mode images for control, DOX and tadalafil +DOX- treated mice. **B and C,** the averaged data of fractional shortening **(B)** and ejection fraction **(C)** in the mice are presented as mean ± S.E. (n = 6 per group; *, $P < 0.05$ versus control; #, $P < 0.05$ versus DOX). Reprinted from Koka, et al. J Pharmacol Exp Ther. 2010 Sep 1;334(3):1023-1030 with permission.

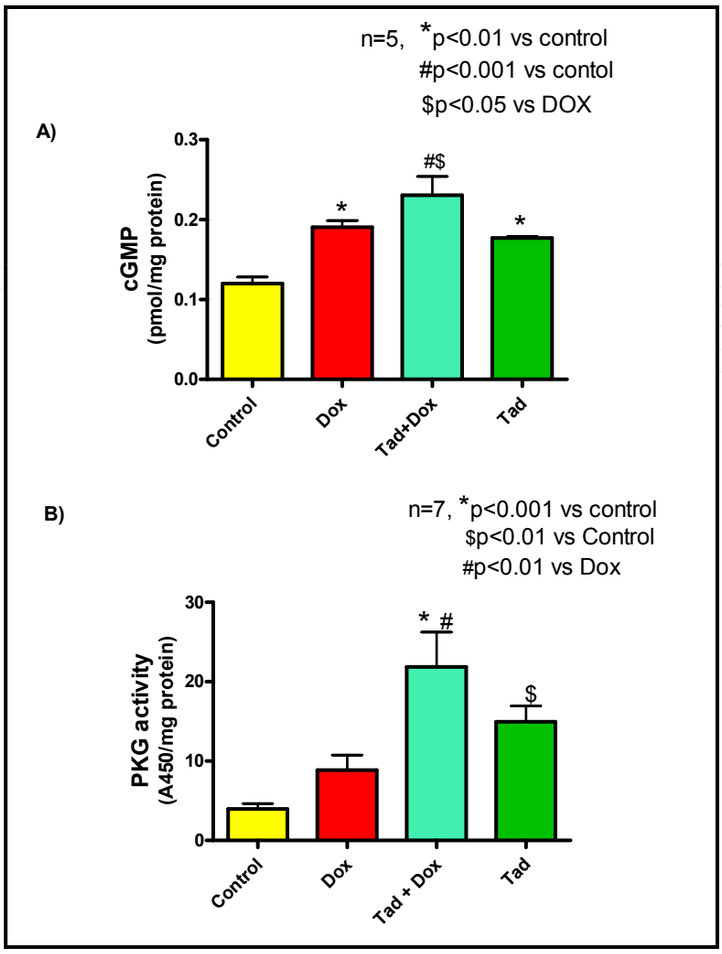

Fig. 3. Tadalafil augments cGMP and protein kinase G after DOX treatment. cGMP level **(A)** and PKG activity **(B)** in the cardiac tissue. Results are presented as mean ± S.E. (n = 5–7/group). *, $P < 0.05$ versus control; #, $P < 0.05$ versus DOX group. Partial data reprinted from Koka, et al. J Pharmacol Exp Ther. 2010 Sep 1;334(3):1023-1030 with permission.

3.3 PDE-5 inhibitors in cancer

Increased PDE-5 expression is reported in multiple human carcinomas including metastatic breast cancers, colon adenocarcinoma, bladder squamous carcinoma, and lung cancers as compared to adjacent normal tissues (Epstein and Hachisu, 1984;Joe *et al.*, 2003;Lim *et al.*, 2003;Piazza *et al.*, 2001;Porst *et al.*, 2001;Singer *et al.*, 1976;Whitehead *et al.*, 2003). PDE-5 was also detected as a predominant isoform of cGMP-PDEs in many carcinoma cells lines in culture, including colonic adenocarcinoma (SW480, HCT116, HT29, T84), breast cancer (HTB-26, MCF-7), lung cancer, bladder and prostate cancer (LNCAP, PC-3), and leukemia (Thompson *et al.*, 2000;Whitehead *et al.*, 2003;Zhu *et al.*, 2005). These studies suggest a functional role of an up-regulated PDE-5 in controlling tumor cell growth and death. PDE-5 selective inhibitors, sildenafil and vardenafil induced caspase dependent apoptosis and antiproliferation in B-cell chronic lymphatic leukemia (Sarfati *et al.*, 2003;Zhu *et al.*, 2005). Vardenafil when given in combination with DOX significantly improved the survival and reduced the tumor size in the brain-tumor-bearing rats (Black *et al.*, 2008). In this study, oral

administration of vardenafil and sildenafil increased the rate of transport of compounds across the blood-tumor-brain and improved the efficacy of DOX in treatment of brain tumors. The selective increase in tumor capillary permeability appeared to be mediated by a selective increase in tumor cGMP levels and increased vesicular transport through tumor capillaries, and could be attenuated by iberiotoxin, a selective inhibitor for calcium-dependent potassium (K_{Ca}) channels, that are effectors in cGMP signaling. This study supported the use of PDE5 inhibitors as a novel therapy to selectively increase drug transport to malignant brain tumors. Another PDE-5 inhibitor, exisulind (sulindac sulfone) and its higher affinity analogues also induced apoptosis and inhibited cell proliferation in colon tumor cells lines by activating PKG and increasing phosphorylation of β-catenin (Lim *et al.*, 2003;Liu *et al.*, 2002a).

One of the major causes of chemotherapy failure in cancer treatment is multidrug resistance (MDR). One of the known causes of MDR is overexpression of the ATP-binding cassette (ABC) transporters, such as P-glycoprotein (ABCB1/P-gp/MDR1), multidrug resistance proteins (ABCCs/MRPs) and breast cancer resistant protein (ABCG2/BCRP). Among these transporters, the ABCB1 transporter is the most important mediator of MDR (Ambudkar *et al.*, 2003), and is responsible for chemotherapeutic drug resistance to a variety of drugs, including vinca alkaloids, anthracyclines, epipodophyllotoxins and taxanes (Szakacs *et al.*, 2006). These transporters actively efflux a variety of structurally and functionally diverse chemotherapeutic drugs out of cancer cells, thereby reducing the intracellular drug accumulation, increasing the likelihood of decreased cytotoxic and thus unsuccessful treatment (Dean *et al.*, 2001;Gillet *et al.*, 2007;O'Connor, 2007). Therefore, a promising approach is to inhibit these transporters to restore the sensitivity of drug-resistant cancer cells to chemotherapeutic drugs, which leads to a more efficacious treatment for cancer patients. As a result, a number of compounds have been identified with the ability to inhibit individual or several transporters by blocking drug efflux, increasing drug accumulation and thus sensitizing resistant cancer cells. Several of these agents, including cyclosporine A, VX-710 (biricodar), Verapamil(Germann *et al.*, 1997;Minderman *et al.*, 2004;Qadir *et al.*, 2005), LY475776 (Dantzig *et al.*, 2004), V-104 and GF-120918 (elacridar) (Evers *et al.*, 2000) can inhibit/suppresses the function of multiple transporters including ABCB1, ABCC1, and ABCG2. Unfortunately, most of these inhibitors have not been translated into clinical trials due to unfavorable side effects, toxic pharmacokinetic interactions, or simply because the magnitude of improvement in therapeutic outcome of these inhibitors with conventional chemotherapeutic agents is either nonsignificant or inconclusive (Szakacs *et al.*, 2006). Several tyrosine kinase inhibitors (TKIs), including imatinib (Shen *et al.*, 2009), nilotinib (Tiwari *et al.*, 2009), lapatinib (Dai *et al.*, 2008), and erlotinib (Shi *et al.*, 2007), can also reverse MDR to antineoplastic drugs mediated by ABC-transporters. However, the reversal potential of these TKIs has not been determined in clinical trials. Consequently, there is an urgent need for the discovery of more efficacious, non-toxic and less expensive novel agents to reverse MDR in cancer cells. Recent study showed that the PDE-5 inhibitor, vardenafil, significantly reversed MDR in ABCB1 overexpressing cancer cells, and its efficacy was greater than that of tadalafil (Ding *et al.*, 2011). Sildenafil also inhibited cell surface ABC transporters ABCB1 and ABCG2-midiated drug efflux, resulting in an increase in the intracellular concentrations of anticancer drugs and ensuing drug sensitivity (Shi *et al.*, 2011). However, sildenafil had no effect on efflux mediated by ABCC1. Based on these

recent studies, it is reasonable to suggest that sildenafil may have the potential to improve the chemotherapeutic outcome of cancer patients by enhancing the distribution and accumulation of chemotherapeutic drugs and ensuing drug sensitivity.

3.4 PDE-5 inhibitors in prostate cancer

All forms of prostate cancer therapy cause significant risk of erectile dysfunction due to trauma sustained by the cavernosal nerves (Rambhatla *et al.*, 2008). As mentioned earlier, PDE-5 is the predominant enzyme in the corpus cavernosum and plays an essential role in vascular smooth muscle contraction through specific regulation of cGMP. There is an increasing amount of evidence suggesting that PDE-5 inhibitors significantly improve erectile function in men after post-radical prostatectomy (Mydlo *et al.*, 2005;Ohebshalom *et al.*, 2005;Schiff *et al.*, 2006;Teloken *et al.*, 2007). Their efficacy and safety have triggered a number of attempts to determine their potential benefits in non-urological conditions (Vlachopoulos *et al.*, 2009). The rationale behind the use of PDE-5 inhibitors on a prolonged and continuous basis in the post-prostatectomy patient has never been fully and scientifically delineated (Rambhatla *et al.*, 2008). The prolonged and continuous administration of vardenafil, prevented both fibrosis and loss of smooth muscle, subsequently reduced corporal veno-occlusive dysfunction (CVOD) following bilateral cavernosal nerve resection (Ferrini *et al.*, 2006). Similar results were reported both in the unilateral and bilateral nerve resection models using continuous long-term administration of sildenafil (Kovanecz *et al.*, 2008a). A long-term single daily dose of tadalafil also prevented CVOD and the underlying corporal fibrosis in the rat caused by cavernosal nerve damage, as effectively as the previously reported continuous treatment with vardenafil or sildenafil, through a cGMP-related mechanism that appeared to be independent of iNOS induction (Kovanecz *et al.*, 2008b). Sildenafil treatment was also effective for improving erectile function in men with post-radiation, particularly, in the early stages after the completion of radiation (Teloken *et al.*, 2007). Treatment with exisulind, another PDE-5 inhibitor, at 250 mg bid had been evaluated in men with prostate cancer following radical prostectomy (Goluboff *et al.*, 2001). In a randomized, 12 month study; exisulind suppressed the overall rise in prostate specific antigen (PSA) levels compared to placebo group. In addition, PSA doubling time was increased more than two fold for high-risk patients who continued with exisulind. Another study also reported that the early use of PDE-5 inhibitor after prostate brachytherapy maintained erectile function at both 6 and 12 months (Pahlajani *et al.*, 2010). Emerging studies focusing on the molecular mechanisms of apoptosis and fibrosis are beginning to shed some light on the beneficial use of PDE-5 inhibitors.

In recent years, extensive and diverse preclinical and clinical studies indicated that PDE-5 inhibitors also had beneficial effects to enhance the chemotherapeutic efficacy of anticancer drugs in prostate and other cancer. PDE-5 inhibitors, sulindac sulfide and exisulind, inhibited growth and induced apoptosis in both the androgen-sensitive (LNCaP) and androgen-insensitive (PC-3) human prostate cancer cell lines (Lim *et al.*, 1999;Lim *et al.*, 2003). Exisulind also suppressed the growth of human prostate cancer cells in a nude mouse xenograft model (Goluboff *et al.*, 1999). At a low dose, combination of colecoxib, a cyclooxygenase-2 (COX-2) inhibitor, with exisulind prevented prostate carcinogenesis by altering key molecular events (Narayanan *et al.*, 2007). Combination of celecoxib and exisulind not only enhanced apoptosis, but also exerted an anti-inflammatory effect by the reduced levels of COX-2, prostaglandin E_2, and tumor necrosis

factor α (TNF-α). Therefore, a combination of potential agents at low doses is considered to be very efficacious in minimizing toxicity compared with the use of individual agents at higher dose levels.

Recently, we demonstrated that co-treatment with the PDE-5 inhibitor, sildenafil, potentiated the antitumor efficacy of DOX in prostate cancer cells, while simultaneously reducing the risk of cardiomyopathy (Das *et al.*, 2010). Cell proliferation of PC-3 and DU145, prostate cancer cells, were reduced in a dose-dependent manner with DOX treatment (Figure 5 A, B). Co-treatment with sildenafil resulted in an additive effect on DOX-induced reduction of cell proliferation (Figure 4 A, B). Co-treatment with sildenafil also enhanced DOX-induced cell killing (Figure 4 C, D). Sildenafil and DOX combination also enhanced the killing of ovarian cancer and sarcoma cells, suggesting a potential efficacy of sildenafil in chemosensitization in multiple malignancies. Co-treatment with sildenafil and DOX enhanced PC-3 and DU145 prostate cancer cell killing through further enhancing ROS generation compared to DOX alone. In contrast, the sildenafil and DOX combination attenuated DOX-induced ROS generation in normal prostate cells. It has been suggested that the basic difference in mitochondrial respiration between normal and cancer cells makes cancer cells more sensitive to oxidative stress (Deberardinis *et al.*, 2008;Vander Heiden *et al.*, 2009). Further investigations need to be warranted to define how sildenafil sensitizes cancer cells to amplify DOX-mediated ROS generation. Interestingly, sulindac, also selectively enhanced killing of cancer cells exposed to oxidizing agents via production of ROS (Resnick *et al.*, 2009). However, low levels of sulindac also induced delayed preconditioning response against I/R injury in the heart through up-regulation of putative effectors of cardioprotection including iNOS and HSP27 (Moench *et al.*, 2009).

We further demonstrated that co-treatment with sildenafil and DOX enhanced DOX-induced apoptosis in PC-3 and DU145 prostate cancer cells (Figure 4 E, F) (Das *et al.*, 2010). The increased apoptosis by sildenafil and DOX was associated with enhanced expression of proapoptotic proteins Bad and Bax and suppression of Bcl-2 and Bcl-xL. Also, sildenafil and DOX combination dephosphorylated Bad, which may enhance Bad heterodimerization with Bcl-xL thereby promoting DOX-induced apoptosis. The ectopic overexpression of Bcl-xL in DU145 cells attenuated the synergistic effect of sildenafil and DOX on cell killing. Caspase-3 and -9 activities were also increased following sildenafil and DOX co-treatment. Overexpression of dominant negative procaspase-9 in DU145 cells blocked the enhanced cell killing by combined treatment with sildenafil and DOX compared with DOX alone.

Treatment with sildenafil and DOX in mice bearing prostate tumor xenografts resulted in significant inhibition of tumor growth (Figure 5A) (Das *et al.*, 2010). The ratio of tumor weight to body weight was also reduced with sildenafil co-treatment with DOX compared to DOX alone (Figure 5B). The reduced tumor size was associated with amplified apoptotic cell death (Figure 6) and increased expression of activated caspase-3. The anti-tumor effect of sildenafil and DOX combination ameliorated DOX-induced cardiac dysfunction, which was consistent with our previous study showing improved left ventricular (LV) function with PDE5 inhibitors (sildenafil and tadalafil) in DOX-treated mice (Fisher *et al.*, 2005;Koka *et al.*, 2010). Fractional shortening (LVFS) and ejection fraction (LVEF) declined in DOX-treated mice. Sildenafil co-treatment with DOX improved LVFS and LVEF compared with the DOX-treated groups.

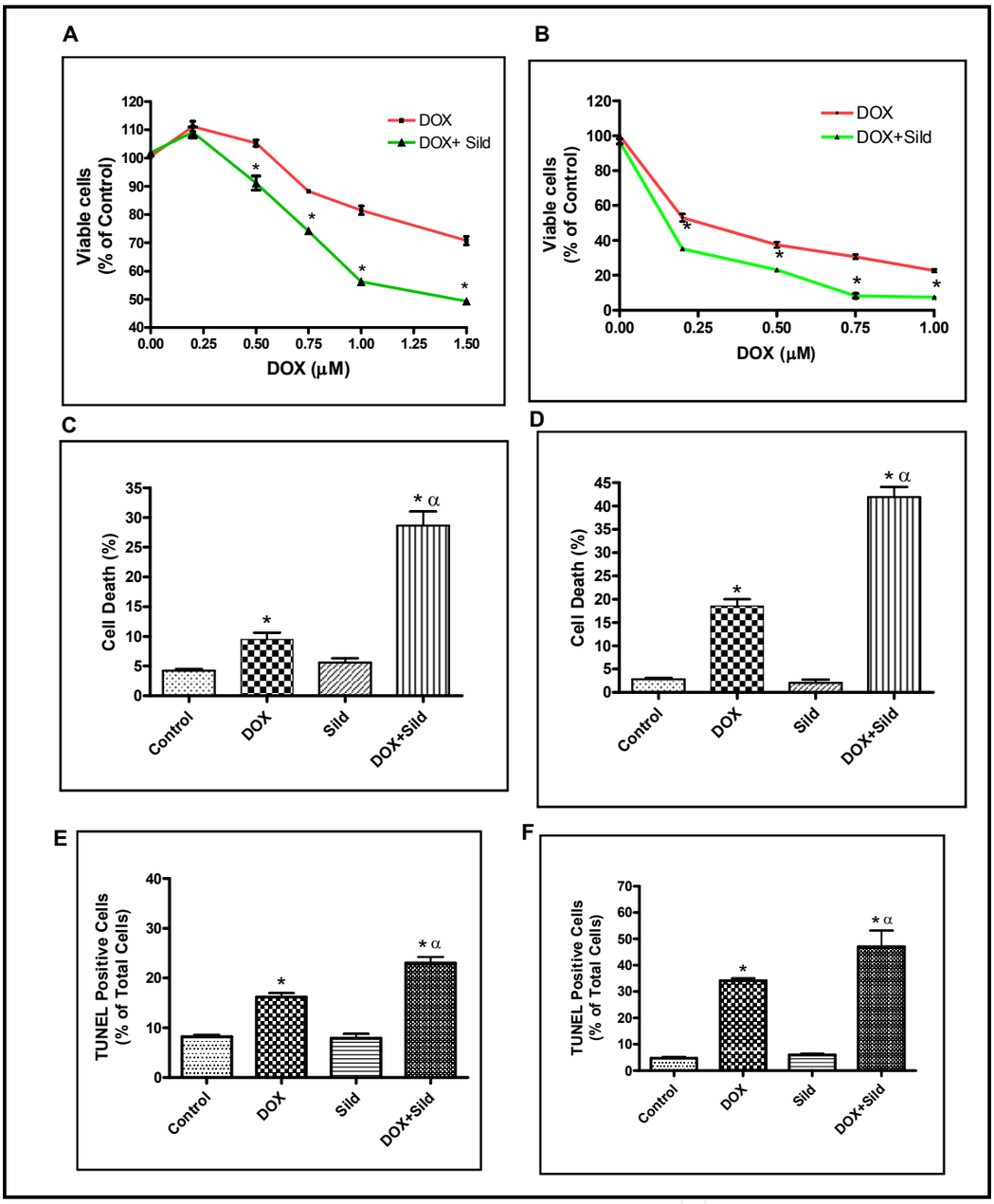

Fig. 4. Sildenafil (Sild) enhances DOX-induced prostate cancer cell death. Cell viability of (A) PC-3 and (B) DU145 cells after 72 h of treatment with different concentrations of DOX and/or sildenafil (10 μM). (*p<0.001 vs respective concentration of DOX; n=6). Cell death assessed after 24 h treatment of (C) PC-3 with 1.5 μM DOX and 10 μM sildenafil and (D) DU145 with 0.5 μM DOX and 10 μM sildenafil (*p<0.001 vs control and $^{\alpha}$p<0.001 vs DOX; n=6). Apoptosis is assessed by TUNEL staining after 72 hr of treatment. Percentage of TUNEL-positive nuclei in (E) PC-3 cells following treatment with 1.5 μM DOX and 10 μM sildenafil and (F) DU145 with 0.5 μM DOX and 10 μM sildenafil (*p<0.001 vs control and $^{\alpha}$p<0.001 vs DOX; n=3). Results are presented as mean ± S.E. Reprinted from Das et al. Proc Natl Acad Sci U S A. 2010 Oct 19;107(42):18202-18207 with permission.

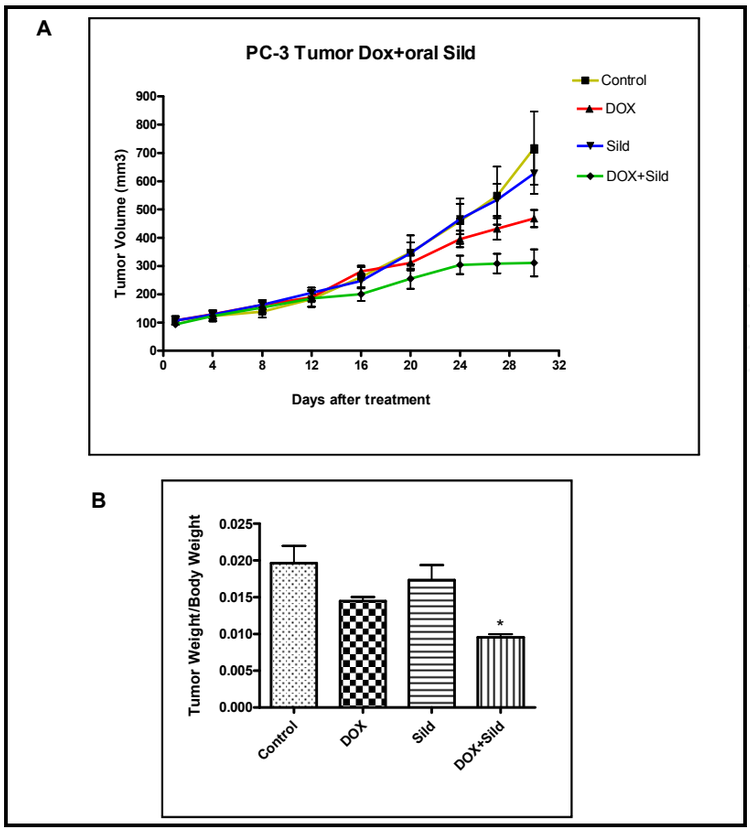

Fig. 5. Oral administration of sildenafil (Sild) potentiates DOX-induced inhibition of prostate tumor xenograft growth. Male nude mice bearing PC-3 human prostate tumors were treated with DOX (3 mg/kg, i.p., twice per week, a total of six times) or sildenafil (10 mg/ kg, orally, everyday) or DOX+sildenfil for 30 days. (A) Tumor growth during 30 d of different treatments (n=8). (B) Bar diagram showing the ratio of tumor weight to body weight after 30 d of treatment (*p<0.05 vs. DOX alone; n=8). Reprinted from Das et al. Proc Natl Acad Sci U S A. 2010 Oct 19;107(42):18202-18207 with permission.

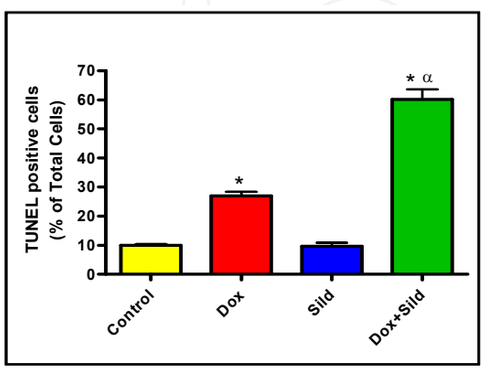

Fig. 6. Sildenafil enhances DOX-induced apoptosis in PC-3 prostate tumors. Bar diagram showing TUNEL-positive cells (*p<0.001 vs. control and $^{\alpha}$p<0.001 vs. DOX; n=3). Results are reported as means ±SE. Reprinted from Das et al. Proc Natl Acad Sci U S A. 2010 Oct 19;107(42):18202-18207 with permission.

4. Concluding comments and future perspective

PDE-5 inhibitors including sildenafil, vardenafil and tadalafil are safe and efficacious first-line on-demand agents for the treatment of erectile dysfunction (Boolell *et al.*, 1996;Porst *et al.*, 2001). Their mechanism of action involves inhibition of the PDE-5 enzyme and resulting increase in cGMP and smooth muscle relaxation in the penis. Their target enzyme, PDE-5 is expressed in several tissues throughout the human body, including the pulmonary and systemic vasculature, hypertrophied myocardium and cancer cells. Preclinical studies have demonstrated that PDE-5 inhibitors have powerful cardioprotective effect in the setting of I/R injury, pressure overload-induced hypertrophy, heart failure and DOX-induced cardiomyopathy. The effects of PDE-5 inhibitors on the pulmonary circulation and hypertrophied right ventricle have made these agents first-line therapy for many patients with pulmonary hypertension. Several reports have indicated that PDE-5 inhibitors improve erectile function following radiation therapy or post-radical prostatectomy in prostate cancer patients. Recent research from our laboratory has reported provocative findings that **sildenafil is both a powerful sensitizer of DOX-induced killing of prostate cancer and provides concurrent cardioprotective benefit (Das *et al.*, 2010).** Moreover, sildenafil and vardenafil have been shown to block or reverse the drug efflux function of the ABC transporters, thereby suggesting that sildenafil can be used as a modulator of ABCB1 and ABCG2 to reverse MDR in cancer cells. Considering the well-established safety profile of PDE-5 inhibitors, clinical studies are needed to fully exploit the beneficial effect of the combination treatment of anti-tumor agents such as DOX with the PDE-5 inhibitors as a therapeutic tool in prostate cancer patients. Also, further studies are needed to gain in depth understanding of the molecular mechanisms by which PDE-5 inhibitors increase the efficacy of chemotherapeutic agents.

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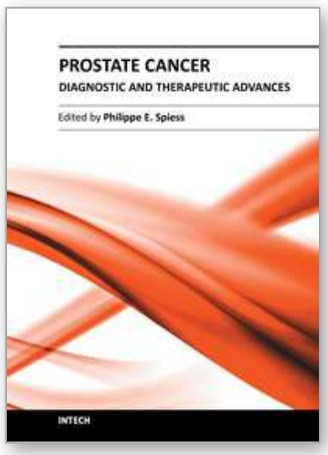

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In this book entitled "Prostate Cancer - Diagnostic and Therapeutic Advances", we highlight many of the significant advances made in our treatment armamentarium of prostate cancer. The book is subdivided into four sections termed: 1) novel diagnostic approaches, 2) surgical treatments options, 3) radiation therapy and its potential sequelae, and 4) medical management and its treatment complications. After reading the present book , readers will be very familiar with the major clinical advances made in our multifaceted treatment approach to prostate cancer over the past decade.This book is a tribute to our pioneering urologists and allied healthcare professionals who have continually pushed forward our traditional therapeutic envelope.

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