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Therapeutic Applications of PARP Inhibitors: Anticancer Therapy and Beyond

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Abstract

The aim of this article is to describe the current and potential clinical translation of pharmacological inhibitors of poly(ADP-ribose) polymerase (PARP) for the therapy of various diseases. The first section of the present review summarizes the available preclinical and clinical data with PARP inhibitors in various forms of cancer. In this context, the role of PARP in single-strand DNA break repair is relevant, leading to replication-associated lesions that cannot be repaired if homologous recombination (HRR) repair is defective, and the synthetic lethality of PARP inhibitors in HRR-defective cancer. HRR defects are classically associated with BRCA1 and 2 mutations associated with familial breast and ovarian cancer, but there may be many other causes of HRR defects. Thus, PARP inhibitors may be the drugs of choice for BRCA mutant breast and ovarian cancers, and extend beyond these tumors if appropriate biomarkers can be developed to identify HRR defects. Multiple lines of preclinical data demonstrate that PARP inhibition increases cytotoxicity and tumor growth delay in combination with temozolomide, topoisomerase inhibitors and ionizing radiation. Both single agent and combination clinical trials are underway. The final part of the first section of the present review summarizes the current status of the various PARP inhibitors that are in various stages of clinical development. The second section of the present review summarizes the role of PARP in selected non-oncologic indications. In a number of severe, acute diseases (such as stroke, neurotrauma, circulatory shock and acute myocardial infarction) the clinical translatability of PARP inhibition is supported by multiple lines of preclinical data, as well as observational data demonstrating PARP activation in human tissue samples. In these disease indications, PARP overactivation due to oxidative and nitrative stress drives cell necrosis and pro-inflammatory gene expression, which contributes to disease pathology. Accordingly, multiple lines of preclinical data indicate the efficacy of PARP inhibitors to preserve viable tissue and to down-regulate inflammatory responses. As the clinical trials with PARP inhibitors in various forms of cancer progress, it is hoped that a second line of clinical investigations, aimed at testing of PARP inhibitors for various non-oncologic indications, will be initiated, as well.

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1. Introduction

1.1. The discovery of PARP and the early benzamide inhibitors

The discovery of poly(ADP-ribose) polymerase (PARP), or as it was called then ADP-ribosyl transferase (ADPRT), goes hand-in hand with anticancer therapy. The first observation, before the enzyme was discovered, was that the earliest chemotherapy agents, the DNA alkylating agents, caused a profound decrease in glycolysis due to depletion of cellular NAD^+ (Roitt, 1956). ADP-ribose polymers were identified shortly afterwards and finally, the enzyme responsible, PARP, was discovered (Chambon et al., 1963). The PARP reaction catalyses the cleavage of NAD^+ into nicotinamide and ADP-ribose leading to the rapid consumption of NAD^+ when DNA is damaged by alkylating agents. The second product of the reaction, nicotinamide, causes a modest product inhibition of the reaction. Based on this knowledge the first PARP inhibitors were the nicotinamide analogues where the heterocyclic nitrogen at the 3 position was replaced with a carbon to generate a benzamide analogue (Purnell and Whish, 1980). Substitutions at this 3 position improved solubility and the 3-substituted benzamides, e.g. 3-aminobenzamide (3-AB) helped elucidate the function of PARP. A pivotal study by Sydney Shall's group (Durkacz et al., 1980) demonstrated that 3-AB inhibited the repair of DNA breaks induced by the DNA alkylating agent, dimethyl sulfate (DMS), and enhanced DMS cytotoxicity. This study was the first to suggest a potential utility of PARP inhibitors in combination with DNA alkylating agents to treat cancer. Of course we now know that there is a family of PARP enzymes but, in terms of DNA repair and its exploitation in cancer therapy, PARP1 and PARP2 are the targets, as these enzymes have overlapping function in the repair of DNA breaks by the base excision repair/single strand break repair (BER/SSBR) pathway (Schreiber et al., 2006). More recently, PARP3 has been shown to co-operate with PARP1 in response to DNA double strand breaks (Boehler, 2011) but the significance of PARP3 inhibition in cancer therapy has not been explored. Most of the inhibitors are active against both PARP1 and 2 and for the rest of this review the term PARP will be used to cover both PARP1 and PARP2.

The initial impetus to the development of PARP inhibitors came from the need to develop tools to study the role of the enzyme and to enhance the activity of DNA damaging agents used to treat cancer, based on the simple principle that if the cytotoxic works by damaging the DNA, repair of that damage presents a resistance mechanism and therefore inhibiting the repair would lead to persistent damage and greater cytotoxicity (Figure 1).

1.1.2 Identification and development of potent inhibitors—Despite providing "proof of principle" data and helping to elucidate the function of PARP, the benzamides were weak; they needed to be used at millimolar concentrations in cell-based studies, which meant they were unsuitable for studies in animals. In addition, they inhibited other cellular pathways (Milam and Cleaver, 1980). Nevertheless, they provided a good starting point for the development of inhibitors with increased potency and virtually all PARP inhibitors in use today have the nicotinamide/benzamide pharmacophore. During the 1990s PARP inhibitors of increasing potency and specificity were discovered using various approaches. Using an analogue by catalogue approach Banasik screened 170 compounds for their inhibitory potency, making a major contribution to inhibitor design (Banasik et al., 1992). This study identified several compounds with potent PARP inhibitory activity including the isoquinolinones, quinazolinones, quinazoline diones, phthalazinones and phenanthridinones, of which 4-amino-1,8-naphthalimide was the most potent. Several of these compounds have been used as leads for subsequent drug development by various groups, for example, the phenanthridinones led to PJ-34 and subsequently INO-1001 that entered clinical trials (Jagtap and Szabo, 2005; Ferraris, 2010). The alternative approach of synthetic chemistry and the development of structure-activity relationships (SAR) led to the identification of 3,4-

dihydro-5-methylisoquinolin-1(2*H*)-one (PD128763) and 8-hydroxy-2-methylquinazolin-4-[3*H*]-one (NU1025), both of which were about 50-fold more potent PARP inhibitors than 3-AB (Suto et al., 1991; Arundel-Suto et al., 1991; Griffin et al., 1995) These inhibitors were more active in cells at 100-200 μM than 3-AB was at 5 mM. The more potent inhibitors identified by both the "analogue by catalogue" and SAR studies all had the carboxamide group of the benzamide pharmacophore rotationally constrained by incorporation into a second ring, indicating that this was critical for improved potency. The reason why these structural features were associated with potency became apparent when structural biology studies were done. Crystallization of PD128763, 4-amino-naphthalimide and NU1025 in the NAD^+ binding site of the PARP1 catalytic domain demonstrated that the carboxamide group made several important hydrogen bonds with Ser904-OG and the Gly863-N in the catalytic domain and its restriction within a heteroring improved the interaction, in line with the prediction from the increased potency (Ruf et al., 1996; Ruf et al., 1998). Based on crystallographic analysis of the binding of 2-(4-hydroxyphenyl)benzamidazole-4-carboxamide (NU1085) several tricyclic lactam indoles and benzamidazoles were developed in which the carboxamide group was held in the favorable orientation by incorporation into a 7-membered ring (Canan-Koch et al., 2002; Skalitzky et al., 2003; Calabrese et al., 2003; Calabrese et al., 2004). These compounds, e.g., AG14361 make critical hydrogen bonds with Gly863 and Ser904, and the important catalytic Glu988 residue (Marsischky et al., 1995). Further development of AG14361 led to the identification of AG-14447 with a Ki of 1.4 nM against PARP1 (Thomas et al., 2007), and it was the phosphate salt of this compound (AG-014699, rucaparib) that was the first PARP inhibitor to enter clinical trial for cancer patients (Plummer et al., 2006; Plummer et al., 2008). Several academic investigators and pharmaceutical companies have had an active PARP inhibitor development program and several have entered clinical investigation such as Veliparib (ABT-888), which also has low nM Ki against both PARP1 and PARP2 (Penning et al., 2009) and olaparib (AZD2281) with nanomolar IC_{50} values against PARP1 and PARP2 (Menear et al 2008; Ferraris, 2010; Javle and Curtin, 2011). Iniparib (BSI-201, 4-iodo-3-nitrobenzamide) has now been shown not to be a PARP inhibitor (Patel et al., 2012a) and data on this compound will not be described here.

1.2. Chemosensitization and radiosensitization

Studies with PARP inhibitors have demonstrated sensitization to ionizing radiation (IR) UV irradiation and a variety of cytotoxic drugs. Some of these may be compound-specific (off target?) or cell line-spec ific but we can have confidence that the enhancement of the cytotoxicity *in vitro* and anticancer activity *in vivo* is due to PARP inhibition when validated by genetic studies. PARP null mice and cells derived from them are hypersensitive to IR, DNA methylating agents and topoisomerase I poisons (Menissier de Murcia et al., 1997; Menissier de Murcia et al., 2003; Masutani et al., 1999; Masutani et al., 2000; Burkle et al., 2000; Smith et al., 2005). It should be noted here that there are subtle differences between PARP-1 deletion and PARP inhibition. Firstly, whilst PARP-1 knockout mice are viable and fertile and PARP-2 knockout mice are also viable and fertile the deletion of both enzymes is embryonic lethal (Menissier de Murcia *et al.* 2003). This is an important consideration as the inhibitors inhibit both enzymes, usually with similar potency and thus inhibition is more similar to the deletion of both enzymes. Secondly, the inhibitors inhibit PARP catalytic activity but not their binding to DNA and, since the enzyme needs to be poly(ADP-ribosyl)ated to dissociate from DNA, it can remain bound causing a physical obstruction to the repair of the break. This was first proposed by Thomas Lindahl in 1992 (Satoh and Lindahl, 1992) who elegantly showed that repair of nicked plasmid DNA by nuclear extracts was not dependent on PARP but if PARP was present NAD^+ as the substrate was necessary for repair, which could be inhibited by 3-aminobenzamide. This indicated that inactive PARP impeded DNA repair and that in the presence of PARP, polymer formation was

necessary for repair to procede. Recently, ChIP experiments demonstrated increased binding of PARP to alkylating agent-damaged DNA in the presence of a PARP inhibitor (Kedar et al 2012) and, similar data derived independently showed increased chromatin binding of PARP when cells were exposed to PARP inhibitors as well as DNA damaging agent, resulting in greater enhancement of cytotoxicity than lack of PARP-1 and PARP-2 (Murai et al 2012). Finally, PARP-1 and PARP-2 may have roles independent of their catalytic activity in gene regulation, for instance, and these factors need to be considered when making predictions about the potential of inhibitors based on data from genetic deletion experiments.

1.2.1 Preclinical studies with DNA methylating agents—Monofunctional DNA methylating agents are the most potent activators of PARP and since the earliest observations with 3-AB (Durkacz et al., 1980) there has been significant interest in the development of PARP inhibitors as modulators of resistance to anticancer DNA methylating agents. DNA methylating agents, currently used in anticancer therapy, include dacarbazine (DTIC) and temozolomide (TMZ), largely used to treat brain tumors and melanoma. These drugs methylate DNA at the O^6-N^7- and position of guanine and the N^3-position of adenine. The excision of these N-methylpurines (N^7-MeG and N^3-MeA) generates a DNA single strand break (SSB) and inactivation of PARP potentiates the effects of TMZ by inhibiting repair of these SSB (Denny et al., 1994; Villano et al., 2009). An early study demonstrated that PD128763 and NU1025 enhanced TMZ-induced DNA strand breakage and increased its cytotoxicity 4- to 7-fold at concentrations 50-100 times lower than the concentration of 3-AB needed for a similar level of potentiation (Boulton et al., 1995). Further investigations demonstrated that the more potent benzimidazole PARP inhibitor, NU1085, at even lower concentrations potentiated TMZ up to 6-fold in a panel of 12 human lung, colon, breast and ovarian cancer cell lines, independently of tissue of origin or p53 status of the cell line (Delaney et al., 2000). The novel and very potent PARP inhibitors have been used at low or sub-micromolar concentrations to potentiate TMZ cytotoxicity in a variety of cell lines. CEP 6800 at only 1 μM potentiated TMZ-induced DNA damage and cytotoxicity in U251MG human glioblastoma cells (Miknyoczki et al., 2003), GPI 15427 (1-2 μM) increased TMZ growth inhibition in human glioblastoma (SJGBM2) cells (Tentori et al., 2003) and in a panel of colon cancer cell lines (Tentori et al., 2006) and a series of potent benzimidazoles and tricyclic lactam indoles, including AG14361, at a concentration of only 0.4 μM, potentiated TMZ-induced growth inhibition of LoVo (human colon carcinoma) by up to 5.3-fold (Calabrese et al., 2003; Calabrese et al., 2004). Recently it was shown that the PARP inhibitor ABT-888 (veliparib) enhanced TMZ cytotoxicity preferentially during S-phase, indicating that an accumulation of replication-associated DSBs were largely responsible for cell death (Liu et al., 2008a; Liu et al., 2008b).

Defects in the DNA mismatch repair (MMR) pathway confer resistance to TMZ (Liu et al., 1996). MMR defects are associated with tumor development (Modrich and Lahue, 1996) particularly hereditary and sporadic cancers of the colon and ovary (Herman et al., 1998). Various PARP inhibitors (3-AB, PD128763, NU1025, AG14361 INO-1001 and ABT-888) enhanced TMZ cytotoxicity to a greater extent in MMR-deficient than MMR proficient cells, including isogenic pairs of MMR proficient and deficient human cancer cells. In some cases this was extended to xenografts, completely overcoming MMR-mediated resistance (Wedge et al., 1996; Tentori et al., 1999; Curtin et al., 2004; Cheng et al., 2005; Horton et al., 2009). Since only tumors lack MMR, PARP inhibition, in combination with TMZ, represents a potentially selective therapeutic approach.

Potentiation of TMZ anticancer activity by various PARP inhibitors has been investigated in a variety of in vivo models. NU1025 and TMZ co-treatment increased the survival of mice with brain lymphomas (Tentori et al., 2002). GPI 15427 increased TMZ-induced tumor growth delay and antimetastatic activity in a B16 melanoma model. This compound crosses

the blood-brain barrier and enhanced the antitumor activity of TMZ in mice bearing intracranial melanomas, gliomas and lymphomas (Tentori et al., 2003). ABT-888 is probably the most studies PARP inhibitors in both *in vitro* and *in vivo* studies it potentiated the activity of TMZ in a variety of subcutaneous, orthotopic and metastatic xenograft models including human lymphoma, ovarian, lung, pancreatic breast and prostate cancer (Palma et al., 2009). It is documented to cross the blood-brain barrier and significantly enhanced the antitumor activity of TMZ in a syngeneic orthotopic rat glioma model, intracranial human primary glioblastoma and in models of breast cancer brain metastases (Donawho, 2007; Clarke et al., 2009; Palma et al., 2009). In models of pediatric cancer rucaparib (AG-014699) enhanced the anti-tumor activity of TMZ in neuroblastoma and medulloblastoma xenografts (Daniel et al., 2009; Daniel et al., 2010). AG14361 caused profound enhancement of TMZ activity against LoVo (human colon cancer) xenografts (Calabrese et al., 2004). Complete tumor regressions have been observed in mice bearing U251MG (human glioblastoma) tumors treated with TMZ and CEP-6800 (Miknyoczki et al., 2003) and in SW620 (human colon cancer) xenografts treated with TMZ in combination with AG14361 and AG14447 (Calabrese et al., 2004; Thomas et al., 2007). It was these latter studies that led to the first anticancer clinical trial of a PARP inhibitor (AG014699/rucaparib) in 2003.

1.2.2 Preclinical studies with topoisomerase I (Topo I) poisons—DNA methylating agents have limited application in cancer chemotherapy compared to the Topo I poisons. Topo I poisons are used in the treatment of a variety of cancers; topotecan is used to treat small cell lung cancer, ovarian and cervical cancer and irinotecan is used in the treatment of colorectal cancer. Topo I catalyzes the transient breakage of DNA to allow unwinding necessary to relieve torsional strain resulting from transcription and replication. Topo I poisons, such as the camptothecins, stabilize the TopoI-DNA cleavable complex in the nicked conformation such that DNA strand breaks, and hence cytotoxicity, correlates directly with Topo I activity. The interest in the use of Topo I poisons in the treatment of cancer comes from the observation that Topo I is elevated in some tumors (Kaufmann et al., 1995). The BER/SSBR pathway is implicated in the repair of Topo I lesions; cells lacking the BER scaffold protein, XRCC1, are hypersensitive to camptothecin (Caldecott and Jeggo, 1991). PARP is thought to participate in this process by recruiting XRCC1 to the site of the Topo I-associated DNA break (El-Khamisy et al., 2003), which in turn recruits tyrosyl DNA phosphodiesterase (TDP 1), which removes Topo I from the DNA (Plo et al., 2003). Additionally, PARP1 is able to interact with Topo I and repair Topo I-associated SSBs (Malanga and Althaus, 2005). Several studies have investigated sensitization of Topo I poisons by PARP inhibitors, in general the levels of sensitization are more modest (around 2 to 3-fold) in comparison to the DNA methylating agents (usually >5-fold)

The earliest study identifying PARP inhibitors as potential sensitizers of Topo I poisons was that of Mattern and colleagues, who showed that 3-AB increased camptothecin cytotoxicity in L1210 cells (Mattern et al., 1987). Camptothecin activated PARP in L1210 cells and NU1025 increased both camptothecin-induced DNA breaks and cytotoxicity (Bowman et al., 1998; Bowman et al., 2001). Subsequently NU1025 and NU1085 were shown to enhance the cytotoxicity of the clinically active Topo I poison, topotecan, in a panel of 12 human cancer cell lines independently of p53 status and tissue of origin (Delaney et al., 2000). Further studies with a variety of the newer PARP inhibitors have also demonstrated potentiation of Topo I poisons: CEP 6800, increased camptothecin-induced DNA damage in HT29 (human colon cancer) cells (Miknyoczki et al., 2003). GPI 15427 enhanced the chemosensitivity of SN-38 (the active metabolite of irinotecan) in a panel of colon cancer cell lines (Tentori et al., 2006). The potent benzimidazoles and tricyclic lactam indoles also potentiated topotecan in A549 (human non-small cell lung cancer) and LoVo cells Calabrese et al., 2003; Calabrese et al., 2004). AG14361 potentiated topotecan-induced growth

inhibition in Lovo, SW620 (human colon cancer) and A549 cells (Calabrese et al., 2004). Further tricyclic lactam inhibitors, including AG14447 (the phosphate salt of which is the clinically active PARP inhibitor, AG-014699, rucaparib), caused sensitization of topotecan in human colon cancer cell lines (Thomas et al., 2007). Proof that AG14361 was acting via inhibition of PARP activity and repair came from the demonstration that it enhanced topotecan activity in PARP wild-type MEFs, but not PARP null MEFs, and increased the persistence of camptothecin-induced DNA breaks (Smith et al., 2005). Similar data was observed with ABT-888 (Veliparib), which increased topotecan cytotoxicity and cell cycle perturbations in a variety of human ovarian, leukemic and lung cancer cell lines and in wild-type MEFs but not PARP1 null MEFS (Patel et al., 2012b). Conflicting data was obtained with deletion or depletion of PARP1 between these two studies with the observation that PARP1 null MEFs were more sensitive to camptothecin (Smith et al., 2005) or similarly sensitive to wild-type MEFs, with no sensitization of human cancer cell lines depleted of PARP1 (Patel et al., 2012b).

The potent PARP inhibitors have been taken into *in vivo* studies with the Topo I poisons, with encouraging results. CEP-6800 caused a 60% enhancement of irinotecan-induced tumor growth delay in mice bearing HT29 xenografts, (Miknyuczki et al., 2003) and the antitumor activity of TMZ+irinotecan against HT29 xenografts was increased by GPI 15427 (Tentori et al., 2006) In this study GPI 15427 decreased irinotecan-induced diarrhea suggesting that the combination might achieve a greater therapeutic index by simultaneously decreasing toxicity and increasing the antitumor activity. In contrast, studies with olaparib resulted in an increase in the toxicity of topotecan, such that the dose needed to be reduced 8-fold to be tolerable (Zander et al 2010). AG14361 increased the irinotecan-induced delay of human colon cancer xenograft growth by 2 to 3-fold without significantly increasing irinotecan-induced body-weight loss (Calabrese et al., 2004) and the clinical PARP inhibitor AG-014699 (rucaparib) enhanced topotecan-induced tumor growth delay in a neuroblastoma model (Daniel et al., 2009). In this latter study, AG-014699 did increase topotecan-induced body weight loss from 2 to 15% in mice bearing NB-1691 tumors but only from 3 to 5% in mice bearing SH-SY-5Y tumors. Thus the toxicity of the combination of topoisomerase I poisons with PARP inhibitor may be dependent not only the drug (irinotecan vs topotecan), the PARP inhibitor (olaparib vs rucaparib) but potentially also the tumor xenograft. Strain differences in the mice may also play a role. These data have implications for the clinical trials with PARP inhibitors where toxicities have been observed using the combination of topotecan and olaparib.

1.2.3 Preclinical studies with ionizing radiation—Radiotherapy is used at some stage in the treatment of around 50% of cancer patients. Ionizing radiation causes a plethora of DNA damage, base modifications, SSB and double-strand breaks (DSB) and it is these latter lesions that are considered the most cytotoxic. Radiosensitization by PARP inhibitors is less marked than chemosensitization, generally <2-fold increase in cytotoxicity. However, with the large number of patients receiving radiotherapy such combinations may be justified.

Early studies revealed that inhibition of PARP led to radiosensitization of mammalian cells (Ben-Hur et al., 1985). Additional studies have demonstrated radiosensitization by a variety of PARP inhibitors (ANI, NU1025, AZD2281, E7016) in multiple cell line models with dose-enhancement ratios of 1.3 to 1.7 (Schlicker et al., 1999; Bowman et al., 2001; Brock et al., 2004; Dungey et al., 2008; Russo et al., 2009). For example, at a concentration that inhibited PARP by >90% 6-[5*H*]-phenanthridinone significantly increased radiation-induced cytostasis and apoptosis (Weltin et al., 1997) and 4-amino-1,8-naphthalimide enhanced ionizing radiation-induced cytotoxicity 1.3 to 1.5 in a panel of human and rodent cell lines (Schlicker et al., 1999). In some studies PARP inhibitors selectively radiosensitize actively replicating S-phase cells (Banasik et al., 1992). It is proposed that the mechanism by which

PARP inhibition increases ionizing radiation sensitivity is by inhibiting the repair of SSBs that convert to DSBs upon collision with replication forks in S-phase (Saleh-Gohari et al., 2005). Such lesions can be visualized by persistence of ionizing radiation -induced γH2AX foci following PARP inhibitor treatment (AZD2281/olaparib and E7016) (Dungey et al., 2008; Russo et al., 2009). These data were supported by the observation that PARP inhibition increased the γH2AX foci and RAD51 foci (indicative of increased homologous recombination at stalled replication forks) (Harper et al., 2010). However, PARP has also been implicated in DSB repair through interaction with non-homologous end joining (NHEJ) and has been shown to exist in a complex with DNA-PKcs and Ku70/80, that are important components of the NHEJ pathway (Mitchell et al., 2009; Spagnolo et al., 2012). In addition PARP is thought to participate in an alternative or back-up NHEJ (A-NHEJ) (Iliakis, 2009).

The growth-arrested cell fraction within a tumor is radioresistant and may re-populating the tumor after radiotherapy (Weichselbaum and Little, 1982; Barendsen et al., 2001). In *in vitro* models to mimic the clinical situation by measuring recovery from potentially lethal damage (PLD), the increased survival of growth-arrested cells is assessed after a recovery period. The dihydroisoquinolinone, PD128763, blocked recovery from PLD and approximately doubled X-ray-induced cell kill in both proliferating and stationary cultures (Arundel-Suto et al., 1991). Similarly, NU1025 prevented PLD recovery in L1210 cells (Bowman et al., 1998). AG14361 also inhibited recovery from PLD in rodent and human colon cancer cell lines, LoVo and SW620 by 70% and reduced DNA DSB repair (Calabrese et al., 2004; Veuger et al., 2003). A panel of tricyclic lactam indoles also inhibited the recovery from PLD irradiation (8 Gy) between 54 and 91% in human colon cancer cells (Thomas et al., 2007). These observations have clinical importance as growth-arrested hypoxic radio-resistant cells can repopulate the tumor after radiotherapy and are a major contributing factor to failure of radiotherapy treatment (Liu et al., 2008a).

Despite the greater technical challenges a number of studies have demonstrated good in *vivo* radiosensitization by PARP inhibitors. In mice bearing SCC7, RIF-1 and KHT sarcomas PD128763 caused an up to 3-fold enhancement of the therapeutic effect of X-rays (Leopold and Sebolt-Leopold, 1992). In combination with fractionated X-rays AG14361 doubled the tumor growth in mice bearing LoVo xenografts (Calabrese et al., 2004) and orally administered GPI 15427 prior to irradiation significantly enhanced the irradiation-induced growth inhibition in HNSCC xenografts (Khan et al., 2010). Most published preclinical studies have been done with ABT-888, which has been shown to significantly increase the anti-tumor activity of ionizing radiation in xenograft models of human colon, lung and prostate cancer (Albert et al., 2007; Donawho 2007; Barreto-Andrade et al., 2011). MK-4827 radiosensitized human lung and triple negative human breast carcinoma xenografts (Wang et al., 2011) and olaparib (AZD2281) in combination with radiotherapy caused significant tumor regression of Calu-6 non-small cell lung carcinoma xenografts when compared to radiotherapy alone (Senra et al., 2011). Patients with glioblastoma multiforme are often given TMZ and radiotherapy together and in mouse models of this patient population, i.e. intracranially implanted human primary gliomas, ABT-888 significantly increased the lifespan of mice receiving TMZ + ionizing radiation (Clarke et al., 2009). The PARP inhibitor E7016, also enhanced the combination treatment of TMZ and irradiation, slowing growth of tumor by an additional 6 days in human glioma xenografts (Russo et al., 2009).

Studies with AG14361 revealed that this PARP inhibitor also increased the transient perfusion of the tumors and, because hypoxia causes radioresistance, the increased oxygenation may have contributed to the *in vivo* radiosensitization (Calabrese et al., 2004). Further investigations revealed that AG14361 and AG014699 (rucaparib) caused

vasodilation of pre-constricted rat arteries *ex vivo* and improved vascular perfusion of tumors *in vivo*, as imaged with fluorescent dyes in a dorsal window chamber model (Ali et al., 2009; Ali et al., 2011), which could contribute to radiosensitization. Using the same model systems olaparib was also subsequently demonstrated to have vasoactive effects *ex vivo* and *in vivo* and enhance the antitumor activity of olaparib against human NSCLC xenografts (Senra et al., 2011). Whether this is a more generalized phenomenon remains to be determined. In addition, the mechanisms responsible for this effect require further characterization.

1.2.4 Preclinical studies with other cytotoxic drugs—There are some sporadic and sometimes conflicting data regarding the ability of PARP inhibitors to potentiate other anticancer cytotoxics. For example, 6(5H)phenanthridinone increased carmustine cytotoxicity in murine but not human lymphoma cell lines and protected human lymphoma cells from doxorubicin (Holl et al., 2000) In contrast, PJ34 increased doxorubicin cytotoxicity to He La cells, but the mechanism was thought to be by increasing topoisomerase II levels, (Magan et al., 2012) and the related compound, INO-1001, increased the anticancer activity of doxorubicin against MDA-MB-231 and MCa-K xenografts *in vivo* (Mason et al., 2008). However, AG014699 (rucaparib) did not increase doxorubicin activity against MDA-MB-231 xenografts (Ali et al., 2011). Such sporadic reports may be compound-specific. There are also conflicting reports regarding the potentiation of platinum agents such as carboplatin and cisplatin by PARP inhibitors. These agents induce inter- and intrastrand crosslinks in DNA, which are repaired by nuclear excision repair (NER) and HRR and are used in the treatment of a variety of tumor types, but most commonly ovarian, lung, testicular and GI cancers. However, BER/SSBR is not usually implicated in the repair of cisplatin-induced DNA damage, and therefore a PARP inhibitor would not immediately be expected to sensitize cells to cisplatin. Nevertheless, PARP1 has been reported to bind to, and be activated by, cisplatin-induced DNA damage (Burkle et al., 1993; Guggenheim et al., 2008) However, PARP1 deleted cells are not reported to be sensitive to platinum agents and the ability of PARP inhibitors to sensitize cells to cisplatin appears to be cell line and compound dependent (Bernges and Zeller, 1996; Guggenheim et al., 2008). For example, in a panel of ovarian cell lines a selection of the potent PARP inhibitors identified originally by Banasik in 1992 all potentiated the DNA methylating agent, MNNG, but none potentiated cisplatin or the bifunctional agent BCNU (Bernges and Zeller, 1996). Evidence is now emerging that PARP inhibitors are preferentially effective with platinum therapy in HRR defective cells, for example AZD2281 (olaparib) selectively sensitized BRCA2 defective cell lines but not BRCA2 proficient cells to platinum therapy (Evers et al., 2008).

This selective sensitization of HRR-defective cells to platinum agents has translated into several *in vivo* studies. The PARP inhibitor ABT-888 (veliparib) in combination with platinum drugs caused regression of BRCA1 and 2-deficient MX-1 xenografts (Donnawho et al., 2007). In a genetically engineered mouse model of hereditary BRCA-associated breast cancer treatment with olaparib (AZD2281) alongside cisplatin or carboplatin inhibited tumor growth although an enhancement of cisplatin toxicity was observed (Rottenberg et al., 2008). Similarly, AG-014699 (rucaparib) increased carboplatin-induced tumor growth delay in mice bearing BRCA2 mutant Capan1 xenografts (Drew et al., 2011a; Drew et al., 2011b). Platinum chemopotentiation by PARP inhibitors in the *in vivo* setting may also be influenced by potential vasoactive/improved drug delivery effects, based on reports that the PARP inhibitors CEP-3000 and BGP-15 enhanced cisplatin-induced tumor xenograft growth delay but failed to enhance cisplatin cytotoxicity in corresponding cell line models (Racz et al., 2002; Miknyoczki et al., 2003) however this hypothesis remains to be confirmed.

1.3 Synthetic lethality of PARP inhibitors in cells and tumors with dysfunctional homologous replication repair (HRR)

Arguably the most exciting use of PARP inhibitors is as a single agent, based on the pioneering studies demonstrating that HRR defective cells and tumor xenografts were hypersensitive to PARP inhibition alone (Bryant et al., 2005; Farmer et al., 2005). Synthetic lethality is a term to describe the combined lethal effect of two genetic variations that are otherwise non-lethal when occurring in isolation. DNA repair mechanisms, developed over millions of years of evolution to cope with the daily onslaught of endogenous and environmental DNA damaging agents, are an example of the potential for synthetic lethality. Many of the pathways have overlapping or compensatory mechanisms - a sort of “belt and braces” approach, such that loss of one component (the belt) leads to reliance on the compensatory component (the braces) such that when both are lost the result is catastrophic. This is particularly pertinent in the cancer arena as dysregulation of the DNA damage response is common and a means to create the genomic instability that is an enabling characteristic of cancer (Hanahan and Weinberg 2011). Loss of one aspect of repair creates the genomic instability that promotes the development of cancer but may need to be compensated for by some other aspect of repair for the viability of the cancer cell. The cancer cell is therefore particularly dependent on the remaining compensatory pathway, “non-oncogene addiction” such that inhibition of this pathway can be a way of specifically targeting cancer cells and in particular exploiting a vulnerability that was responsible for the initiation of the cancer in the first place.

In the case of the synthetic lethality between PARP inhibitors and HRR defects the proposed mechanism is that inhibition of the repair of endogenously generated DNA SSBs in the presence of a PARP inhibitor, leads to collapsed replication forks and replication-associated DSBs that require HRR for repair. In the absence of HRR these lesions prove lethal either because they persist or they can only be repaired by alternative error-prone pathways including non-homologous end joining (NHEJ) and single strand annealing (SSA) resulting in gross genomic instability and cell death (Figure 2). The use of PARP inhibitors in this synthetic lethal manner exploits the molecular pathology of cancer cells. Since HRR defects are relatively common in tumors (Kennedy and D’Andrea, 2006; Cerbinskaite 2012) but not normal tissues (with the exception of Fanconi’s anemia patients) this is likely to be a tumor-specific therapy.

The initial studies demonstrated that cells lacking BRCA2, XRCC2, XRCC3 or which had BRCA2 depleted by siRNA, were hyper sensitive to a panel of PARP inhibitors (3-AB, NU1025 and AG14361) (Bryant et al., 2005). Additionally, BRCA1 and BRCA2 defective mouse embryonic stem cells were sensitive to the PARP inhibitors KU0058948 and KU0058684 (Farmer et al., 2005). BRCA dysfunction can arise without mutation in spontaneous cancer (Turner et al., 2004) and epigenetic silencing of BRCA1 function also leads to hypersensitivity to PARP inhibition (Drew et al., 2011a; Drew et al., 2011b). HRR is a complex process involving several components including ATM, ATR, CHK1, MRN (MRE11/RAD50/NBS1), several FANC proteins and RAD51 and its homologues. The loss of any one of these components can confer HRR dysfunction and cause PARP inhibitor sensitivity. Further to the original paper showing that defects in XRCC2 and XRCC3 (both RECA/Rad51 family) (Bryant et al., 2005) renders cells exquisitely sensitive to PARP inhibition, subsequent literature demonstrates that depletion of other components of the HRR pathway also confers hypersensitivity to PARP inhibitor-induced cytotoxicity (McCabe et al., 2006). Other proteins, such as EMSY and PTEN are also implicated as they may regulate other components of the pathway (Cousineau and Belmaaza, 2011). *PTEN* is one of the most commonly mutated tumor suppressors in human cancer and its loss or disruption conferred sensitivity to the PARP inhibitor olaparib, in a panel of human cell lines and to ABT-888 in astrocytes (Mendes-Pereira et al., 2009; McEllin et al., 2010).

However, recent data suggests that PTEN loss is not a universal indicator of PARP inhibitor-induced sensitivity (Hunt et al., 2012; Frazer et al., 2012). PTEN is involved in the phosphoinositide-3 kinase (PI-3K) pathway and recent data suggests that inhibitors of PI-3K increase DNA damage and reduce RAD51 focus formation, indicating a negative impact on HRR, and act synergistically with PARP inhibitors to increase antitumor activity in BRCA-1-related breast cancer models *in vivo* (Juvekar et al., 2012). Furthermore, in models of triple negative breast cancer without BRCA mutations PI-3K inhibition down-regulated BRCA and led to sensitivity to olaparib (Ibrahim et al., 2012). Other studies show that CDK1 regulated BRCA1 activity (Johnson et al., 2009) and that CDK1 inhibition also increased the sensitivity of lung cancer cells, xenografts and spontaneous lung cancers in mice to the PARP inhibitor, AG-014699 without significant toxicity (Johnson et al 2011). These data offer exciting possibilities for the combination of PARP inhibitors with other molecularly targeted agents.

Resistance to PARP inhibitors may arise in BRCA mutant tumors. CAPAN-1 pancreatic cancer cells have a frame shift mutation, 6174delT, rendering them HRR defective and unable to form damage-induced RAD51 foci and exquisitely sensitive to PARP inhibitors. PARP inhibitor-resistant Capan-1 clones acquired the ability to form RAD51 foci after PARP inhibitor treatment or exposure to irradiation due to the intragenic deletion of the 6174delT mutation and restoration of the open reading frame (Sakai et al., 2008; Edwards et al., 2008), with similar reverting mutations observed to restore BRCA1 function (Swisher et al., 2008). In addition, recent cell-based data suggests that in an HRR-defective background PARP inhibition promotes error-prone NHEJ and that an intact NHEJ and 53BP1 pathway is needed for synthetic lethality (Bouwman et al., 2010; Bunting et al., 2010; Patel et al., 2011). These data have recently been confirmed in animal models where depletion of 53BP1 conferred resistance to olaparib in BRCA1 mutant mammary carcinomas (Jaspers et al 2012) Loss of 53BP1 appears to be relatively common in triple negative and BRCA1 mutant breast cancer samples (Bouwman et al., 2010).

Screening for BRCA1/2 mutation may identify cancer patients who could benefit from monotherapy with PARP inhibitors. However, with the potential for other components of the HRR to be lost or mutated in cancer and the loss of BRCA1 through epigenetic mechanisms all conferring sensitivity to PARP inhibition, as well as the confounding effects of NHEJ defects conferring resistance in BRCA mutated tumors, there are likely to be many false negatives and positives using this approach. The challenge is therefore to develop biomarkers that will identify HRR dysfunctional tumors likely to respond to PARP inhibitor therapy. Gene expression profiling has been used to identify a BRCA-like phenotype in ovarian cancer (Konstantinopoulos et al., 2010). Alternatively, evidence of gross genomic instability identified by array comparative genomic hybridization (array CGH) may reflect HRR dysfunction (Vollenbergh et al., 2011). A logistically challenging approach, but one that should identify cells that are HRR dysfunctional, whilst not having a high false positive rate, is to measure HRR function in fresh, viable, patient tumor material. RAD51 focus formation after DNA damage (a necessary step in HRR downstream of BRCA1, BRCA2 and the most commonly mutated HRR genes) can be used as an indication of ongoing HRR. This approach has been used to identify HRR function in AML, ovarian cancer ascites cells and breast cancer biopsies (Gaymes et al., 2009; Willers et al., 2009; Mukhopadhyay et al., 2010). Importantly, AML, MDS and ovarian cancer ascites cells with reduced ability to form Rad51 foci also display hypersensitivity to PARP inhibition (Gaymes et al., 2009; Mukhopadhyay et al., 2010). Interestingly, the ovarian study found that 50% of samples were HRR defective compared to the expected rate of 10-15% BRCA mutation carriers, highlighting the need for biomarkers of HRR function rather than reliance on BRCA mutation screening (Mukhopadhyay et al., 2010). This approach may be possible on fixed tissues as in FFPE breast cancer biopsies obtained at surgery after neoadjuvant

chemotherapy showed it was possible to detect RAD51 foci in replicating (geminin-staining) cells (Graeser et al., 2010).

1.4 Clinical studies with PARP inhibitors

In 2003, in Newcastle-upon-Tyne, UK, the first dose of a PARP inhibitor (AG-014699, rucaparib) was given to a cancer patient. Since then there has been a major leap forward in the development of these novel agents with now at least nine inhibitors in various stages of clinical trial development, with or without pharmacodynamic (PD) investigations. PD markers to measure the effect of PARP inhibition include PAR formation in tumor tissue and peripheral blood mononuclear cells as well as assessment of γ-H2AX foci. PARP inhibitor development pipelines are pursuing two therapeutic applications: (1) PARP inhibitors to potentiate chemotherapy or radiotherapy; and (2) PARP inhibitors as single agents to selectively kill cells with inherited or acquired defects in HRR. The pre-clinical data clearly indicate that different doses and schedules are needed for these two applications of PARP inhibitors, and similar results are being observed clinically. Higher doses and longer exposure periods are required for single agent activity both in cell culture and animal studies preclinically. This is because PARP activity needs to be suppressed pretty well completely to render the inhibition of levels of endogenous damage cytotoxic, and that the suppression needs to be long enough for the cells to have all gone through at least one S-phase in order for unrepaired SSB to collapse replication forks. For chemo-and radiopotentiation, where high levels of damage are induced in a short period PARP does not need to be totally suppressed for such levels of damage to be cytotoxic. If high doses of PARP inhibitor are used in combination with a cytotoxic agent they are likely to cause host toxicity. This can be deduced by the comparison of concentrations and doses of PARP inhibitors used in the literature for single agent versus chemosensitizing activity. For example, 400 nM AG-014699 (rucaparib) is more than adequate to achieve substantial chemo- and radiosensitization human cancer cell lines in vitro and 1 mg/kg daily x 5 in combination with TMZ is the efficacious and maximum tolerated dose *in vivo* (Thomas et al 2007). Compare this with up to 7 μM AG-014699 (rucaparib) needed to inhibit the survival of BRCA mutant human cancer cells by 50% *in vitro* and 10 to 25 mg/kg for up to 6 weeks needed for significant tumor growth delay in mice bearing BRCA mutant xenografts, and that doses of 50 mg/kg are completely non-toxic as a single agent in BRCA heterozygote and wild type mice (Drew et al 2011). Thus a doses and schedules of single agent PARP inhibitor determined as safe in Phase I clinical trials are likely to be highly toxic when given in combination with anticancer cytotoxic chemotherapy. Conversely, a dose and schedule determined as safe in combination with a cytotoxic is unlikely to be sufficient as a single agent.

In PARP inhibitor/chemotherapy combinations toxicity; particularly increased myelosuppression, is a limiting factor. The most exciting potential use of PARP inhibitors is as single agents in germline *BRCA* mutated cancers and more recently in the treatment of high-grade serous ovarian cancers. The possibility that many other cancers also have HRR defects that may be exploited by PARP inhibition, if biomarkers can be developed to identify them, is tantalizing. The clinical trials with various classes of PARP inhibitors are summarized in Table 1.

1.4.1 PARP inhibition in combination therapy—The first clinical trial, initiated in 2003, was based on the promising preclinical activity of AG014361 and AG-014699 in combination with TMZ (Calabrese et al., 2004; Thomas et al., 2007). This Phase I trial involved a Phase 0 component where the pharmacokinetics (PK) of AG014699 (rucaparib) and pharmacodynamic assays of its activity were performed following a single dose of a PARP inhibitor prior to the TMZ-combination as well as during the combination treatment.

A 50% reduction in PARP activity was the target PARP-inhibitory dose (PID) in this study (Plummer et al., 2008). AG014699 showed linear PK with no interaction with TMZ. AG014699 was escalated without any serious adverse events and the PID was estimated at 12 mg/m^2, based on 74% to 97% inhibition of PARP activity in peripheral blood mononuclear cells (PBMCs). An increase in DNA breakage in PMCs was also observed and there was a >50% PARP inhibition in tumor biopsies post-treatment. The recommended phase II dose was 200 mg/m^2 of TMZ with 12 mg/m^2 of AG014699. However, this combination in a phase II study in metastatic melanoma caused en hanced TMZ-induced myelosuppression, necessitating a 25% dose reduction of TMZ. Nevertheless, despite the reduced dose of TMZ, the study reported an increase in the response rate and median time to progression compared to historical reports of TMZ alone (Plummer et al., 2006). Dose-limiting myelosuppression was also noted in a phase I trial of INO-101 with TMZ (Bedikian et al., 2009) and in a trial of olaparib in combination with DTIC (dacarbazine, which is enzymatically degraded to the same DNA methylating species as TMZ) in melanoma patients. Disappointingly, in this study there was no clinical benefit over dacarbazine alone when given in combination with olaparib (Khan et al., 2011).

A few Phase I studies in combination with Topo I poisons have been conducted, largely to determine the MTD and proof of mechanism. In a Phase I study of ABT-888 (veliparib) with topotecan myelosuppression was observed but after further preclinical studies informed a revised schedule the MTD was established as topotecan 0.6 mg/m^2/d with ABT-888 10 mg twice daily on days 1-5 of a 21 day schedule. In this study PARP activity was reduced in both tumor and PBMCs and, importantly, increased DNA breaks were detected in circulating tumor cells and PBMCs and some disease stabilization was observed (Kummar et al., 2011). In a study of veliparib (ABT-888) in combination with irinotecan DLTs were diarrhea and neutropenia with a MTD of 100 mg/m^2 irinotecan (LoRusso et al., 2011). In a phase I study of olaparib and topotecan DLTs of neutropenia and thrombocytopenia were seen following doses of topotecan 1 mg/m^2/daily for 3 days and olaparib 100 mg twice daily so further dose levels were not explored (Samol et al., 2012).

Iniparib showed good activity with gemcitabine and carboplatin in triple negative breast cancer patients and, before it was confirmed that this drug does not inhibit PARP, a clinical trial of olaparib in combination with gemcitabine and cisplatin, sponsored by the National Cancer Institute (NCI) was undertaken. However a DLT of myelosuppression was reported at the first dose level and patients who had not has myelosuppressive therapy were selected for subsequent investigation. PARP activity was reduced in lymphocytes and tumor specimens and the PK of olaparib was affected by gemcitabine. Of the 21 evaluable patients responses were seen in 2, one was a woman with ovarian cancer with a BRCA1 mutation of unknown significance and the other was a man with pancreatic cancer with a known BRCA2 mutation (Rajan et al., 2012).

Clinical trials are finally underway to explore the role of PARP inhibitors in combination with radiotherapy (www.clintrials.gov) but no final results have been published yet. The appeal of such studies is that the toxicities seen with the chemotherapy combinations may be avoided as the treatment is targeted. An interim report on a phase I trial of ABT-888 (veliparib) in combination with whole brain radiotherapy (37.5 Gy in 15 fractions or 30 Gy in 10 fractions) in patients with brain metastases from advanced solid tumors showed that up to 200 mg veliparib twice daily was well tolerated with radiotherapy and further dose escalation is planned (Mehta et al., 2012).

1.4.2 PARP inhibitors as single agent therapy—The first report of a clinical trial of a PARP inhibitor as a single agent in patients with BRCA mutations was the pivotal phase I study of the oral PARP inhibitor olaparib (Fong et al., 2009a; Fong et al., 2009b). Olaparib

was well tolerated in all patients, toxicities were < grade 3 in severity and did not increase in the BRCA mutation carriers. The MTD was determined as 400 mg olaparib twice daily and PARP inhibition was confirmed in surrogate and tumor tissue. Anti-tumor activity was reported in 12 of the 19 evaluable *BRCA1* and *2* mutation carriers, including patients with breast, ovarian and prostate cancer but no responses were observed in non-*BRCA* mutation carriers. Given these interesting preliminary data, two multicenter, international phase II studies of olaparib exclusively in breast or ovarian cancers patients with BRCA 1 or 2 mutations were conducted. One cohort of 27 patients received 400 mg of olaparib twice daily for 28 days, and the other cohort of 27 patients received 100 mg of olaparib twice daily. In the breast study the overall response rate was 41%(11/27) and progression free survival (PFS) of 5.7 months with 400 mg, but the response rate was lower (22%) with 100 mg (Tutt et al., 2010) as was the PFS (3.8 months). In a parallel study in 55 BRCA mutated carriers with ovarian cancer the overall response rate of 33% in the 400 mg group, and 12.5% in the 100 mg group indicating a dose-dependency of the response (Audeh et al., 2010). The common adverse effects were mild, including fatigue, nausea and vomiting.

Several other PARP inhibitors are currently being investigated in patients with germline *BRCA* mutations. Preliminary reports of a phase I trial of MK-4827, in patients with advanced solid tumors enriched for *BRCA* mutated cancers established a MTD of 300 mg daily with continuous dosing and reported a partial response rate of 20% (12/60) (Schelman et al., 2011). Interim results of the Phase II trial of single agent rucaparib in patients with *BRCA*-mutated breast and/or ovarian cancer reported a clinical benefit rate (CBR) of 34% (Drew et al., 2011b).

The preclinical data suggests the potential for PARP inhibitors as single agents beyond patients with BRCA mutations. Clinical studies are now underway investigating the efficacy of PARP inhibitors in non-germline *BRCA*-mutated cancers, in particular high-grade serous ovarian cancers (HGSOC) and triple negative breast cancer (TNBC). In a four-arm phase II correlative study of continuous olaparib dosing at 400 mg twice daily in HGSOC patients with BRCA mutations compared to those with unknown BRCA status and of BRCA-mutated breast cancer compared with TNBC patients with unknown BRCA status, (Gelmon et al., 2011). Curiously, no responses were observed in the two breast cancer arms but in the patients with non-germline BRCA mutated HGSOC there was response rate of 24% compared with 41% in the confirmed BRCA mutation ovarian cancer patients. This is the *first* study to show single agent PARP inhibitor activity in non-germline BRCA mutated cancers, indicating that sporadic HGSOC could be targeted with PARP inhibitors. PARP inhibitors are now being investigated as maintenance therapy in HGSOC. Preliminary results from patients with platinum sensitive, HGSOC randomized on a 1:1 basis to olaparib 400 mg twice daily or placebo until disease progression showed a significant benefit in PFS (8.4 vs. 4.8 months) favoring the maintenance olaparib (Ledermann et al., 2011; Oza et al., 2011).

2. Beyond anticancer therapy: stroke, circulatory shock, cardiac ischemia

2.1. Introduction, historical perspective and current trends

Historically, much of the early PARP research (1970's-80's) focused on DNA repair mechanisms, and, consequently, anti-cancer therapy became the primary direction for the clinical translation of PARP inhibitors (Shall, 1983; Berger et al., 1987; Graziani and Szabo, 2005). As discussed in the previous section, starting from the early 2000's, this line of work has progressed into multiple clinical trials. From the mid 90's, however, a new direction has also emerged. Recognizing the role of PARP as a potential mediator of cytotoxicity elicited by reactive nitrogen species in the mid 90's produced a new wave of studies and expanded the roles of PARP into many forms of non-oncologic diseases. Initial studies in stroke

(Zhang et al., 1994) and autoimmune diabetes (Radons et al., 1994), recruited many new investigators into the field of PARP. Soon, studies were initiated into many non-oncological directions including neurological diseases, local and systemic inflammatory diseases, metabolic diseases and cardiovascular diseases (overviewed in Szabo and Snyder, 2000; Virag and Szabo, 2002). This expansion (Figure 1), which was, in no small part, also aided by the availability of PARP1 deficient mice, became a direct stimulus for the synthesis and development of new classes of PARP1 inhibitors of various structural classes. These included novel phenanthridinones such as PJ34 (Jagtap et al., 2002), isoquinolones, isoquinolinones (Jagtap et al., 2004; Jagtap et al., 2005) and many additional classes of PARP inhibitors with low micromolar to nanomolar potency. However, most of these new, non-oncological indications have not yet resulted in clinical studies. In fact, with the exception of Phase I studies and small pilot trial of INO-1001 in myocardial infarction (Morrow et al., 2009), all of the on-going clinical development of PARP inhibitors focuses on various areas of oncology.

The continuing primary focus on oncological indications is explained, in part, by novel discoveries identifying novel, crucial roles of PARP1 in DNA repair, for instance in cancers with BRCA mutations (Rios and Puhalla, 2011; Wang et al., 2012). Moreover, the remarkable preclinical efficacy of many of the new-generation PARP inhibitors in animal models of cancer has further guided the field in this direction (see previous section). Cancer is an obvious choice as the therapeutic options for many forms of cancer are limited; the clinical prognosis remains poor and therefore new drugs (especially targeting new pathways) are badly needed. Moreover, in general terms, oncology represents a natural choice for novel, first-in-class drugs (especially ones that have the potential to influence DNA repair processes), as the risk-benefit ratio is clearly the most advantageous. The safety “package” necessary for the introduction of new anti-cancer drugs are more forgiving (when compared to the safety profile expected from drugs designed for non-life-threatening indications); the expected duration of treatment is relatively short for cancer, and suboptimal pharmacokinetic profile of a development compound (such as low oral bioavailability and/or short terminal half-life) can be overcome by systemic (e.g. intravenous infusion) administration.

While the field of oncology has witnessed the clinical introduction of PARP inhibitors over the last decade, the ‘beyond’ fields have progressed as well. As detailed in the subsequent sections, recent studies have shed new light on the molecular mechanisms of PARP-related cell death and PARP-associated inflammatory processes. Such processes are relevant for various forms of neurological, inflammatory and cardiovascular diseases. In addition, PARP inhibitors of various classes have demonstrated marked therapeutic efficacy in many clinically relevant large animal models of non-oncological disease. Moreover, clinical studies have began to explore the process of PARP activation in specimens obtained from human patients. Importantly, new research has shed light on several PARP-related genetic polymorphisms in various neurological and inflammatory diseases, which may be used to guide future experimental therapy (Table 2). It is our expectation that clinical success in the field of oncology will eventually guide the clinical expansion of the new generations of specific PARP inhibitors into various non-oncological diseases. The indication choices are multiple and include many clinical unmet needs. Some of these potential non-oncological indications have poor prognosis that is comparable or worse than most cancers.

The sections below do not attempt to overview the myriads of indications where PARP inhibitors have been reported to exert beneficial effects in preclinical models of neuroinjury, neuroinflammation, neurotrauma, cardiovascular diseases, metabolic diseases, local and systemic inflammatory diseases, pulmonary diseases, and many others. Details of the role of PARP in these conditions is summarized in specialized review articles (Szabo and Dawson,

1998; Szabo, 1998a; Virag and Szabo, 2002; Szabo et al., 2004; Cuzzocrea, 2005; Woon and Threadgill, 2005; Graziani and Szabo, 2005; Jagtap and Szabo, 2005; Koh et al., 2004; Koh et al., 2005; Komjati et al., 2005; Obrosova and Julius, 2005; Virag, 2005; Pacher and Szabo, 2005; Pacher and Szabo, 2007; Kauppinen and Swanson, 2007; Pacher and Szabo, 2007; Kauppinen and Swanson, 2007; Pacher and Szabo, 2008, Moroni, 2008; Gero and Szabo, 2008; David et al., 2009; Szabo, 2009; Peralta-Leal et al, 2010; Giansanti et al., 2010; Szabo and Modis, 2010; Sodhi et al., 2010; Ba and Garg, 2011; Laudisi et al., 2011; Luo and Kraus, 2012). Table 2 presents a partial summary of disease conditions where the preclinical data have begun to translate into human/clinical evaluation. In the current review, we focus on a limited list of disease indications, where, in our view, the unmet need for a novel therapeutic agent is the greatest, the preclinical data showing the importance of the PARP pathway are most convincing, and the likelihood of timely clinical translation appears most feasible.

2.2 Inhibiting PARP to mitigate the side-effects of cytotoxic drugs

As overviewed in the preceding chapters, PARP inhibitors have the potential to become a new form of therapy for many forms of therapy-resistant cancers. In addition, several lines of data (using either PARP deficient mice or pharmacological PARP inhibitors) suggest PARP inhibitors may have additional uses to mitigate the cytotoxic side effects of various cytotoxic drugs, including drugs used in oncology. While the results summarized in the section below are intriguing, we must, nevertheless, emphasize that this concept remains to be tested in the clinical arena, and, in fact, the current clinical experience points towards the opposite effect (PARP inhibitors, in fact, can enhance the cytotoxicity of several drugs; see previous sections). Thus, the “jury is out” on the clinical translatability of this concept.

2.2.1. Doxorubicin—The first example for PARP inhibitors to mitigate the side effects of an antitumor agent derives from studies involving doxorubicin, a “classic” anticancer anthracyclin, which also happens to be a “classic” inducer of dose-limiting cardiotoxicity (Aubel-Sadron et al., 1984). Since increased oxidative stress is a major factor implicated in the cardiotoxicity of doxorubicin, in 2004 we hypothesized that the activation of PARP1 may contribute to doxorubicin-induced cardiotoxicity. To explore this possibility, we subjected $PARP1^{+/+}$ and $PARP1^{-/-}$ mice to a single intraperitoneal injection of doxorubicin (25 mg/kg). Five days after doxorubicin administration, left ventricular performance was significantly depressed in $PARP1^{+/+}$ mice, but only to a smaller extent in $PARP1^{-/-}$ ones. Similar experiments were conducted in BALB/c mice treated with a PARP inhibitor PJ-34. Treatment with a PJ34 significantly improved cardiac dysfunction, increased the survival of the animals and reduced the doxorubicin-induced increase in the serum lactate dehydrogenase and creatine kinase activities in the heart (Pacher et al., 2002a). Based on these data and on follow-up studies utilizing PARP inhibitors of different classes (Szenczi et al., 2005; Pacher et al., 2006; Mukhopadhyay et al., 2009), it was concluded that PARP activation contributes to the cardiotoxicity of doxorubicin and it was hypothesized that PARP inhibitors may exert protective effects against the development of severe cardiac complications associated with the doxorubicin treatment. Several follow-up studies confirmed and extended the original findings, and delineated some of the molecular mechanisms of the cytoprotection afforded by PARP inhibitors. For instance, it was demonstrated that doxorubicin cardiotoxicity in mice is associated with an increase in myocardial apoptosis, iNOS expression, nitric oxide and mitochondrial superoxide generation, 3-nitrotyrosine formation, MMP2/9 gene expression and PARP activation. At the same time NOX1, NOX2, p22phox, p40phox, p47phox, p67phox, xanthine oxidase, eNOS and nNOS expression remained unchanged, and catalase and glutathione peroxidase activities showed a decrease (Mukhopadhyay et al., 2009). All these effects of doxorubicin were markedly attenuated by peroxynitrite scavengers, which also protected against the

doxorubicin-induced functional deterioration of the heart (Pacher et al., 2003; Shuai et al., 2007; Mukhopadhyay et al., 2009). These findings indicate that peroxynitrite - a toxic oxidant species produced by the reaction of nitric oxide and superoxide (Pacher et al., 2005a; Szabo et al., 2007; Pacher et al., 2007) is a proximate cause of doxorubicin-induced PARP activation in the heart.

The molecular mechanism of doxorubicin-induced cytotoxicity was further explored in the cardiac-derived H9c2 myoblasts and in human coronary artery endothelial cells (Mukhopadhyay et al., 2009). In these experimental model systems, too, doxorubicin dose-dependently increased mitochondrial superoxide and nitrotyrosine generation and apoptosis/necrosis. The doxorubicin-induced apoptosis/necrosis positively correlated with intracellular nitrotyrosine formation, and was prevented by peroxynitrite scavengers. The doxorubicin-induced cell death and nitrotyrosine formation was also attenuated by selective iNOS inhibitors or in iNOS knockout mice (Mukhopadhyay et al., 2009). Finally, various NO donors if co-administered with doxorubicin, but not alone, dramatically enhanced doxorubicin-induced cell death with concomitant increased nitrotyrosine formation and decreased mitochondrial superoxide generation (Mukhopadhyay et al., 2009). These findings identify, peroxynitrite as a major trigger of doxorubicin-induced cell death. This suggests the modulation of the pathways leading to peroxynitrite generation, or its effective neutralization, can be of significant therapeutic benefit. An improvement in therapeutic index is likely because neutralization of this pathway does not produce any decrease in the antitumor effect of doxorubicin, as demonstrated either by the peroxynitrite decomposition catalyst FP15 (Pacher et al., 2003; Bai et al., 2004) or the clinical-stage PARP inhibitor AG014699 (Ali et al., 2012). There are now several studies, using PARP inhibitors (including BGP-15 and INO-1001) of different structural classes confirming the cardioprotective effect against doxorubicin cardiotoxicity *in vitro* and *in vivo* (Pacher et al., 2006; Bartha et al., 2011a).

While there is no disagreement about the notion that PARP inhibition *does not* interfere with the antitumor effect of doxorubicin, here is some disagreement in the literature as to whether PARP inhibition actually *enhances* the anti-tumor effect of doxorubicin. *In vitro* and *in vivo* data with AG014699 (Ali et al., 2012) show no enhancement, while *in vitro* data with PJ34 or INO-1001 in HeLa cells, in human hepatic cancer cell lines and in p53-deficient breast cancer lines indicate that there may be some synergy (Mason et al., 2008; Munoz-Gomez et al., 2011; Magan et al., 2012). The only currently completed human study which utilized PARP inhibitor/doxorubicin combination was a Phase II study with olaparib, where cardiac side effects of doxorubicin have not been reported (Kaye et al., 2012). We hypothesize that the lack of reported cardiotoxicity may be related to the dose of doxorubicin used, or the form of the compound (liposomal PEGylated form, as opposed to the regular form of the drug).

It is interesting to mention that preliminary clinical observations, as well as experimental studies in mice indicate that doxorubicin therapy, in itself, is able to reduce PARP1 activity (Zaremba et al., 2010). The mechanism and the potential clinical implications of these findings remain to be elucidated in future studies.

Another interesting, novel line of investigation focuses on the potential pathogenic role of the “minor” PARP isoform, PARP2. While the mechanism of the cytoprotective effects of PARP1 inhibitors typically involves inhibition of PARP overactivation, prevention of cellular energetic deficit and protection of overactivation of kinase pathways, the protection elicited by PARP2 inhibition appears to involve a modulation of the sirtuin pathway. Studies by Bai and co-workers demonstrated that $PARP2^{-/-}$ mice and aortic smooth muscle cells generated from them display partial protection against doxorubicin toxicity, without

affecting free radical production, DNA breakage and PARP activation. Genetic deletion of PARP2 resulted in the induction of the SIRT1 promoter and consequently increased SIRT1 expression, which, in turn, enhanced mitochondrial biogenesis, which is the putative mechanism involved in the protection by PARP2 deficiency against doxorubicin-induced mitochondrial damage (Szanto et al., 2011).

2.2.2. Cisplatin—A commonly used anticancer agent that suffers from severe, dose-limiting kidney toxicity is cisplatin, frequently used to treat many forms of cancers, including gastrointestinal. Recent work by Pacher and colleagues demonstrated that PARP activation plays a central role in cisplatin nephrotoxicity (Mukhopadhyay et al., 2011). Using a well-established mouse model of nephropathy, the studies demonstrated that genetic deletion or pharmacological inhibition of PARP1 (by two different inhibitors, PJ34 or 5-aminoisoquinoline) markedly attenuated the cisplatin-induced histopathological damage (tubular necrosis) and impaired renal function (elevated serum blood urea nitrogen and creatinine levels). Furthermore, PARP inhibition normalized the inflammatory response (leukocyte infiltration; TNF-α, IL-1β, F4/80, adhesion molecules ICAM-1/VCAM-1 expression) and consequent attenuation of oxidative/nitrative stress (4-HNE, 8-OHdG, and nitrotyrosine content; NOX2/NOX4 expression) (Mukhopadhyay et al., 2011).

The above studies were subsequently confirmed by an independent group, which demonstrated that cisplatin-induced kidney damage (histological, as well as biochemical markers of injury) was attenuated in $PARP1^{-/-}$ mice, as compared to corresponding wild-type animals (Kim et al., 2012). The protection was also seen after inhibiting PARP in wild-type mice with PJ34 treatment (Kim et al., 2012). This study, besides confirming the suppression of inflammatory gene expression (including Il1b, Il6, Il18, Ccl2, Ccl5, Cxcl1, and Cxcl10 gene), also reported that PARP deficiency prevented the upregulation of TLR4. TLR4 is the receptor for endotoxin and other PAMPs (pathogen-associated molecular patterns) and for certain DAMPs (endogenously produced, damage-associated molecular patterns) (Kim et al., 2012). In the context of cisplatin nephrotoxicity (sterile inflammation/organ dysfunction), it is conceivable that the down-regulation of TLR4 is relevant as it protects the cells from the cytotoxic effect of endogenously produced DAMPs (such as the nuclear protein HMGB1), which is released during cell necrosis and damages neighboring cells by activating TLR4.

All of the above responses were linked to an inhibition of pro-inflammatory pathway activation (NF-κB and MAP kinase pathway). In subsequent studies using primary cultures of proximal kidney epithelial cells, it was demonstrated that PARP inhibition exerts its effects primarily by inhibiting necrosis, rather than apoptosis (Kim et al., 2012). This confirmed and extended previous observations demonstrating the same effect of PARP inhibitors in cells challenged with cytotoxic oxidants (Virag et al., 1998a; Virag et al., 1998b; Ha and Snyder, 1999).

Thus, emerging data indicate that PARP activation plays an important role in cisplatin-induced kidney injury, and its pharmacological inhibition may represent a potential approach to preventing the cisplatin-induced nephropathy.

2.2.3. Imatib—There are a limited number of studies investigating the potential protective effect of PARP inhibitors on the cytotoxicity of other anticancer agent. One recent study worth emphasizing is a study, where the effect of the PARP inhibitor, BGP-15, was studied on the cardiotoxic effect of imatinib mesylate (Gleevec) in a Langendorff rat heart perfusion system (Sarszegi et al., 2012). The cytostatic agent suppressed cardiac high-energy phosphate levels, which was prevented by BGP-15. Furthermore, imatinib mesylate treatment-induced activation of MAP kinases (including ERK1/2, p38, and JNK) and the

phosphorylation of Akt and GSK-3beta, which were also suppressed by BGP-15 (Sarszegi et al., 2012).

2.3. PARP inhibition for acute neuroinjury

2.3.1. Stroke—The first indications that PARP activation may be involved in neuroinjury or neurotoxicity derive from *in vitro* experiments conducted by Cosi and colleagues (Cosi et al., 1994) and Snyder and colleagues (Zhang et al., 1994) in the early-to-mid 90's. These studies were, in fact, some of the first experiments that took the field of PARP beyond DNA repair and oncology, and started the explosion that led to discoveries into the role of PARP in cardiovascular, inflammatory and metabolic diseases. Ischemia/reperfusion injury of the brain is frequently modeled in the laboratory by exposing primary neuronal cultures to glutamate or its agonists, or to various reactive oxygen species, NO donors, peroxynitrite or by combined oxygen-glucose deprivation. In cerebellar granule cells, glutamate was found to induce a rapid increase in poly (ADP-ribose) immunoreactivity (Cosi et al., 1994) and similar results were found in primary cortical cultures (Zhang et al., 1994). In a separate line of studies, PARP inhibitors have been shown to protect in these models of brain injury – both in models where injury was induced by glutamate and in response to chemical compounds that generate NO. The rank order of potency of different classes of PARP inhibitors correlated with the degree of protection (Zhang et al., 1994). In addition, primary cortical cultures from $PARP^{-/-}$ mice were found resistant to toxicity from NMDA (a neurotoxic compounds which generates oxyradicals and NO) as well as to the neurotoxicity elicited by combined oxygen-glucose deprivation (Wallis et al., 1993; Cosi et al., 1994; Zhang et al., 1994; Zhang et al., 1995; Wallis et al., 1996; Eliasson et al., 1997).

The pathophysiological relevance of these observations was demonstrated in subsequent, *in vivo* studies, showing that increased poly (ADP-ribosylation) occurs in the ischemic/reperfused brain (Endres et al., 1998a; Endres et al., 1998b). Moreover, in $PARP1^{-/-}$ mice a markedly reduced infarct volume is observed after transient middle cerebral artery occlusion (Endres et al., 1997; Eliasson et al., 1997). ADP-ribose formation was increased and NAD^+ was decreased following focal ischemia in wild-type tissue, while no poly(ADP-ribose) formation is observed in $PARP^{-/-}$ tissue and NAD^+ levels were spared (Endres et al., 1997; Eliasson et al., 1997). A subsequent study confirmed and extended these findings: $PARP^{-/-}$ mice were protected from stroke, while after the viral transfection of wild-type PARP1, the protection from MCA occlusion was lost (Goto et al., 2002).

Over the decade that followed, a large number of additional rodent studies compared the reductions in infarct volume in response to various application regimens and PARP inhibitors of various structural classes (overviewed in Komjati et al., 2005; Moroni, 2008) and established the magnitude of the therapeutic effect, as well as the therapeutic window of intervention. This latter parameter is extremely important, because, most stroke patients arrive with an occluded blood vessel to the hospital, the testing of protective drugs is essential in post-treatment models, both in permanent and transient stroke experiments. The therapeutic window of intervention is substantial (up to 4-6 hours after the onset of ischemia in the middle cerebral artery ischemia-reperfusion models), as demonstrated by a variety of PARP inhibitors including nicotinamide, PJ-34, INO-1001, FR247304, DR2313, NU1025, MP-124, ONO-1294H, KCL-440 and various thienyl-isoquinolone derivatives (DAMYIQ and HYDAMTIQ) (Ducroq et al., 2000; Ayoub and Maynard, 2002; Abdelkarim et al., 2001; Ferraris et al., 2003; Komjati et al., 2004; Iwashita et al., 2004a; Iwashita et al., 2004b; Kamanaka et al., 2004; Ikeda et al., 2005; Nakajima et al., 2005; Haddad et al., 2006; Kaundal et al., 2006; Hamby et al., 2007; Haddad et al., 2008; Kauppinen et al., 2009; Faraco et al., 2010; Egi, 2011; Ikeda et al., 2011; Moroni et al., 2012; Haddad et al., 2012). The beneficial effect of PARP inhibition can be long lasting, i.e. neurological functional

improvements have been shown to persist until at least 6-12 weeks post-ischemia (Kauppinen et al., 2009; Moroni et al., 2012).

Although the incidence of stroke patients over age 75 is equal in men and women, mortality is almost double in women in this age group. This suggests that stroke and stroke related mortality may be influenced by gender and age. Several lines of studies indicate that hypoxia-ischemia activates PARP1 in neonatal brain, and that the involvement of PARP in the pathogenesis of stroke-associated neuroinjury is strongly dependent on the gender of the animal (Eliasson et al., 1997, Hagberg et al., 2004, McCullough et al., 2005; Liu et al., 2009; Yuan et al., 2009; Liu et al., 2011).

Studies investigating PARP and stroke have demonstrated multiple modes of neuroprotective action for various PARP inhibitors. The original list of mechanisms invoked in the neuroprotection, such as direct inhibition of excitotoxicity and cell necrosis downstream from excitotoxin-induced calcium overload, NO and ROS production (Cosi et al., 1994; Zhang et al., 1994; Szabo and Dawson, 1998; Pieper et al., 1999; Mandir et al., 2000; Ying et al., 2002; Du et al., 2003a; Ying et al., 2005; Hamby et al., 2007; Duan et al, 2007; David et al, 2009) and inhibition of pro-inflammatory mediator production (Ullrich et al., 2001; Koh et al., 2004; Hassa et al., 2006; Kraus, 2008; Kauppinen et al., 2009) has been extended with several additional mediators. For instance, recent data demonstrated that interaction between endogenous TWEAK (tumor necrosis factor-like weak inducer of apoptosis) and Fn14 (fibroblast growth factor inducible 14) mediates hypoxia-induced neuronal death *in vitro*, and *in vivo* in rodent stroke models, and emerges as a proximate cause of PARP activation (Haile et al., 2010). Moreover, it was demonstrated that the suppression of the neuroinflammatory response by PARP inhibition leads promotion of new neuron formation (Kauppinen et al., 2009). Furthermore, PARP inhibition has been demonstrated to result in an inhibition of the translocation of the cell death factor AIF (apoptosis-inducing factor) (Yu et al., 2002; Komjati et al., 2004; Culmsee et al., 2005). The formation of free poly(ADP-ribose), which acts as an independent death signal in certain models of neuroinjury is inhibited (Andrabi et al., 2006; David et al., 2009; Siegel and McCullough, 2011; Andrabi et al., 2011). Furthermore, PARP inhibition results in inhibition of matrix metalloproteinase activation (Koh et al., 2005) and protection against the breakdown of blood-brain barrier (Lenzser et al., 2007), suppression of brain edema (Strosznajder et al., 2003) and, possibly, suppression of HMGB1 release from the damaged neurons (overviewed in Moroni, 2008). It is highly likely that all of these above processes form a positive feedback cycle of injury (this concept is overviewed in Jagtap and Szabo, 2005; Chiarugi and Moroni, 2008); hence, interruption of these cycles produces multiple benefits.

Perhaps the most crucial recent development in the field of PARP/stroke was the extension of the proof of concept of efficacy from rodent models to large animal models, including non-human primates. In 2011 Matsuura and colleagues reported their findings with the PARP inhibitor MP-124 in cynomolgus and rhesus monkeys subjected to permanent or transient ischemic stroke models (Matsuura et al., 2011). The study evaluated cerebral infarcts and neurological deficits and explored different doses, timings of administration, as well as potential gender differences. MP-124 markedly reduced neurological deficits and cerebral infarct volumes, as assessed at 28 h after permanent occlusion in a dose-dependent manner (at doses of 0.3, 1 and 3 mg/kg/h intravenous infusion) (Maximal reduction in infarct volume: 64%). The effects were noted in both the cortex/white matter and the striatum. Importantly - and in contrast to several rodent studies; see below - the ameliorative effects of MP-124 were observed in female as well as male monkeys. The effect of the PARP inhibitor was not only gender-independent, but also presented with an attractive therapeutic time window: when the neurological deficits and cerebral infarct volumes were

assessed at several time points after middle cerebral artery occlusion, it was found that treatment with MP-124 at 3 and 6 h post-occlusion remained effective in significantly ameliorating not only the neurological deficits but also the infarct volume. The beneficial effects remained detectable at 3 days and even at 30 days post-infarction (Matsuura et al., 2011). As discussed elsewhere (Ford and Lee, 2011), there is a certain degree of nihilism and stagnation in the field of experimental therapy of stroke (which resembles, to some degree, the field of circulatory shock; see below). Decades of disappointing experience with failed clinical trials in patients with stroke culminated in a reexamination of the process by which candidate drugs are translated to human stroke trials within a conference of industry representatives and academicians known as Stroke Therapy Academic Industry Roundtable (STAIR). STAIR came up with a set of recommendations for the preclinical development of acute ischemic stroke therapies and declared the need for: 1) defining the therapeutic time window in a well-characterized experimental model of stroke; 2) using blinded, physiologically-controlled reproducible studies; 3) measuring both histological and functional outcomes assessed acutely and long-term; 4) testing in rodent models, followed by gyrencephalic species; and 5) using both permanent and transient occlusion models. In this context, it is reassuring to emphasize that the study by Matsuura and colleagues appears to satisfy these criteria, and may represent a milestone in the clinical translation of PARP inhibitors for stroke therapy.

In general, another element generally needed for translating a novel therapy into human trials is evidence that the pathway in question is relevant in human disease. As presented in Table 2, there are several lines of human evidence implicating PARP in stroke. For instance, Activation of PARP in post-mortem brain sections from patients who have died from stroke (Love et al., 1999; Love et al., 2000; Sairanen et al., 2009). Interestingly, the highest PARP1 immunoreactivity was seen in the periinfarct area. Consistently with the results of the preclinical studies, nuclear PARP1 showed a good correlation with the degree of neuronal necrosis (Sairanen et al., 2009).

Overall, in our opinion, the case for the clinical translation of PARP inhibitors for the experimental therapy of stroke is particularly strong. Stroke is a devastating disease, with limited therapeutic options. The duration of PARP inhibitor therapy in stroke is expected to be short, and the PARP inhibitor can be given intravenously. (These factors, in general, present with lower regulatory and drug development hurdles than, for example, the challenges associated with developing and testing an orally bioavailable drug candidate for longer-term use). Nevertheless, we must keep in mind that in human beings (as opposed to experimental animal models), stroke develops on the basis of underlying vascular disease (hypertension, diabetes, hyperlipidemia, etc.) One of the major underlying mechanisms of injury relates to endothelial dysfunction, vasospasm and atherosclerosis. Emerging data indicate the potential role of PARP in the development of endothelial dysfunction associated with a variety of vascular diseases including diabetes, hypertension, aging, and hypercholesterolemia/early stage of atherosclerosis. However, these therapeutic directions are in the realm of chronic administration for prevention (as opposed to treating the consequences of acute ischemic stroke). As discussed in Section 3, this therapeutic direction presents several sets of distinct challenges, and will be much harder to translate into clinical practice than approaches involving acute treatment of stroke with PARP inhibitors.

2.3.2. Traumatic brain injury (TBI)—All of the pertinent translational considerations we have made in the previous section for stroke (unmet clinical need; need for new therapies, especially ones targeting novel pathways; strong preclinical data implicating PARP; data confirming PARP activation in human patients; multiple failed clinical trials and a clear reticence of the field to attempt new clinical trials) can also be made for neurotrauma.

Several lines of studies demonstrated that massive DNA breakage occurs reported after traumatic brain injury (TBI) (Rink et al., 1995; Colicos and Dash, 1996; LaPlaca et al., 1999; Satchell et al., 2003). Consequently, peroxynitrite production and poly(ADP-ribosyl)ation co-localize in areas of necrosis in the traumatically injured neuronal tissues (Scott et al., 1999; Besson et al., 2003). PARP activation occurs as early as 30 minutes after the onset of the trauma and its activation persists for several days (LaPlaca et al., 1999; Besson et al., 2003). Satchell and co-workers studied protein nitration, as a marker of peroxynitrite production, and poly(ADP-ribosyl)ation for 21 days after controlled cortical impact in mice. Both were found to be persistently increased compared with normal brain, with relative peaks seen at 8 and 72 hours (Satchell et al., 2003). The most likely interpretation of these findings is that the unrepaired DNA single-strand breakage maintains a prolonged pattern of PARP activation.

Similar to studies in stroke, some of the early interventional studies utilized either PARP deficient mice (which show a remarkable degree of protection in brain trauma models) (Whalen et al., 1999; Whalen et al., 2000) or the prototypical PARP inhibitor, 3-aminobenzamide (3-AB) and other benzamide derivatives. These compounds were found to be neuroprotective on the neurological deficit and the brain lesion after closed head injury in mice and after TBI induced by fluid percussion, and remained effective in the delayed therapeutic regimen (2 hours) (Besson et al., 2003). Subsequent studies using more potent and more specific inhibitors - such as GPI-6150, INH_2BP, PJ34, INO-1001 - confirmed and extended these early observations (LaPlaca et al., 2001, Satchell et al., 2003; Lacza et al., 2003; Besson et al., 2005 Clark et al., 2007; Du et al., 2007). For instance, the above studies established that the protective effect of PARP inhibition on neurological function lasts up to 21 days (Besson et al., 2003; Satchell et al., 2003). Similarly, the efficacy of various PARP inhibitors has been established in various experimental models of spinal cord injury (LaPlaca et al., 2001; Scott et al., 2001; Scott et al., 2004; Genovese et al., 2005, Lescot et al., 2010; d'Avila et al., 2012). Furthermore, direct, pharmacological supplementation of NAD^+ ameliorated damage in a rodent model of brain trauma (Won et al., 2012). In brain trauma models, as with stroke, PARP inhibition not only attenuated the early stage of neuroinjury, but also to suppressed the degree of the subsequent neuroinflammatory response (d'Avila et al., 2012).

PARP activation has also been demonstrated in human neurotrauma studies. PARP activity is present in neurons of pericontusional tissue of patients suffering from severe TBI (Ang et al., 2003). Specific, poly(ADP-ribosylated) proteins have been identified using proteomic approaches (Satchell et al., 2003; Lai et al., 2008; Fink et al., 2008). In mitochondrial homogenates from brains of rats subjected to traumatic brain injury, several distinct peptide spots were positively identified using MALDI-MS: Complex III (cytochrome c reductase, core protein), Complex IV (cytochrome oxidase, subunit Va), and Complex V (b subunit of F1F0 ATPase); mitochondrial chaperone proteins heat-shock protein 60 (Hsp60) and glucose regulated protein 75 (Grp75); the anion channel VDAC-1; and the mitochondrial inner membrane protein, mitofilin (Lai et al., 2007). It is conceivable that PARylation of electron transport chain proteins affects oxygen consumption and mitochondrial function (Lai et al., 2008; Modis et al., 2011); further studies for delineating the functional role of these reactions is underway.

Recent studies have identified relevant polymorphisms in PARP1 in the context of neurotrauma. Clark and colleagues have investigated whether tagging single nucleotide polymorphisms (tSNPs) covering multiple regions of the PARP1 gene are related to outcome after TBI in humans (Sarnaik et al., 2010). DNA from 191 adult patients with severe TBI was assayed for four tSNPs corresponding to haplotype blocks spanning the PARP1 gene. Categorization as favorable or poor outcome was based on Glasgow Outcome

Scale score assigned at 6 months. The different polymorphisms were correlated with the amount of poly-ADP-ribose-modified proteins in cerebrospinal fluid. In multiple logistic regression analysis controlling for age, initial Glasgow Coma Scale score, and gender, the AA genotype of SNP rs3219119, which tags a haplotype block spanning the automodification and catalytic domains of the PARP 1 gene, was an independent predictor of favorable neurologic outcome. A second SNP (rs2271347), which tags a haplotype block spanning the automodification and catalytic domains of the PARP 1 gene, correlated with the amount of PARylated proteins in the cerebrospinal fluid, but did not correlate with the clinical outcome (Sarnaik et al., 2010). From these findings it can be concluded that after severe brain trauma in humans, a PARP1 polymorphism within the automodification-catalytic domain is associated with neurological outcome, while a polymorphism within the promoter region is associated with poly(ADP-ribose)-modified protein level. The latter may represent a genotypephenotype relationship between PARP1 polymorphism within the promoter region and enzyme activity. Interestingly, the study has also identified gender differences, which are in line with other preclinical and clinical studies. Namely, males were 2.62 times more likely to have poly(ADP-ribose) levels above the median than were females after comparable degree of brain trauma, indicating that female gender in humans may attenuate the degree of PARP activation (Sarnaik et al., 2010).

Overall, in our opinion, the case for the clinical translation of PARP inhibitors for the experimental therapy of neurotrauma is almost as strong as the case for stroke. Similar to stroke, we are dealing with a devastating disease, with limited therapeutic options. Similar to stroke, the duration of PARP inhibitor therapy is expected to be short, and the PARP inhibitor can be given intravenously. As opposed to stroke (where the onset of the blood vessel occlusion is not always clear, and many patients do not present in the hospital until several hours or even days after the onset of the first clinical symptoms), the onset of neurotrauma is generally well defined, and the patients are hospitalized in a rapid fashion. Taken together, neurotrauma presents a potential indication for the future clinical introduction of PARP inhibitors in the not-so-distant future.

2.3.3. Additional central nervous system indications—There are multiple lines of preclinical data that support additional indications in the central and peripheral nervous system for the experimental therapy of PARP inhibitors. As discussed in the Section 3, most of these indications are chronic, and would require long-term, oral therapy in a clinical setting, and hence we believe that the clinical translatability is more remote than in the case of stroke and acute neuroinjury. For reasons of completeness, we briefly discuss some of them below.

The first group of these indications can be classified as “neurodegenerative diseases”. As early as 1999, in MPTP-induced Parkinson’s disease models the role of PARP activation was demonstrated, both using pharmacological inhibitors and PARP deficient mice (Mandir et al., 1999; Cosi and Marien, 1999). This work was subsequently extended to implicate the role of apoptosis-inducing factor and of p53 in the mode of PARP inhibitors’ action (Mandir et al., 2002; Wang et al., 2003; Iwashita et al., 2004; Yokoyama et al., 2010). Moreover, PARP activation was also demonstrated in cadaveric brain sections from patients who died of Parkinson’s disease (Table 2). Clearly, multiple lines of preclinical data support the pathogenetic role of PARP in Parkinson’s disease as well as several other forms of neurodegeneration (e.g. Wang et al., 2007; Mester et al., 2009; Li et al., 2012).

The second group can be classified as “neuroinflammatory diseases” with EAE (experimental allergic encephalomyelitis) being the most studied one (and one that most investigators consider an adequate preclinical model of multiple sclerosis). In murine models of EAE, several studies demonstrated the protective effects of PARP inhibitors

(Scott et al., 2001; Chiarugi, 2002; Scott et al., 2004; Wu et al., 2008; Cavone et al., 2011) and the protection was subsequently confirmed in a primate model in the marmoset (Kauppinen et al., 2005). In contrast, the data with PARP1-deficient mice yielded conflicting results; in one study $PARP^{-/-}$ mice were protected (Farez et al., 2009), while in another study PARP deficiency actually accelerated the onset and severity of the disease (Selvaraj et al., 2009). It is possible that PARP1 plays different roles in the disease in the induction phase vs. the disease progression phase. Nevertheless, based on the PARP1 inhibitor studies multiple lines of preclinical data support the pathogenetic role of PARP1 in EAE (a model of multiple sclerosis) as well as several other forms of neuroinflammation (e.g. Diestel et al., 2003; Burguillos et al., 2011; Tu et al., 2011; Cavone and Chiarugi, 2012).

2.4. PARP inhibition for circulatory shock

The first studies implicating the role of PARP activation and the beneficial effect of PARP inhibitors in various forms of circulatory shock were conducted almost as early as the initial studies into the role of PARP in stroke. Already in 1996, *in vitro* studies established that the pro-inflammatory bacterial cell wall component LPS (endotoxin, bacterial lipopolysaccharide) results in the activation of PARP in cultured macrophages, and the ensuing cytotoxicity is suppressed by PARP inhibitors (Szabo et al., 1996a; Zingarelli et al., 1996a).

Subsequent studies focused on the role of PARP in the development of vascular contractile failure associated with circulatory shock. This phenomenon is closely related to overproduction of NO within the blood vessels due to the expression of the inducible NO synthase within the vascular smooth muscle cells (Szabo, 1995; Kilbourn et al., 1997). In studies in anesthetized rats, inhibition of PARP with the early-generation PARP inhibitors 3-aminobenzamide and nicotinamide was found to reduce the endotoxin-mediated suppression of the vascular contractility of the thoracic aorta in *ex vivo* experiments (Szabo et al., 1996b; Zingarelli et al., 1996b; Tatasargil et al., 2005). However, it should be noted here that nicotinamide inhibits vasoconstriction and stimulates the relaxation of pre-constricted arteries in other models (Hirst et al 1994, Ruddock et al 2000, Ruddock and Hirst 2004). Nicotinamide is used to improve tumor blood flow and oxygenation in radiotherapy trials (Thomas et al 1996, Kaanders et al 2002) and recent evidence suggests that clinically active PARP inhibitors are also vasoactive (Ali et al 2009, Senra et al 2011) Another key feature of circulatory shock is the development of endothelial dysfunction (impaired ability of the vascular endothelium to produce NO, followed by a tendency for local vasospasm, extravasation and edema, increased adhesion and transmigration of mononuclear cells into inflamed organs) (Szabo, 1995; Huet et al., 2001). Early studies demonstrated the protective effects of 3-aminobenzamide against the development of endothelial dysfunction in vascular rings obtained from rats with endotoxic shock (Szabo et al., 1996b; Szabo et al., 1997a; Cuzzocrea et al., 1997). The molecular mechanism by which oxidant stress and PARP activation induces endothelial dysfunction is likely to be related, at least in part, to a PARP-mediated down-regulation of endothelial NADPH levels (Garcia Soriano et al., 2001).

Treatment of rodents subjected to various models of circulatory shock with early-generation PARP inhibitors reduced the infiltration of activated mononuclear cells to various organs, attenuated oxidative and nitrosative stress, and produced improved survival (Szabo et al., 1996b; Zingarelli et al., 1996b). The early results using LPS were subsequently extended to studies using newer generation, more potent inhibitors of PARP and into more clinically relevant rodent model of shock (murine model of cecal ligation and puncture), where both PARP inhibitors of various structural classes, and $PARP^{-/-}$ phenotype produced significant survival benefits and improved vascular function and organ function (Osman et al., 1998; Wray et al., 1998; Oliver et al., 1999, Kühnle et al., 1999; McDonald et al, 2000; Mabley et

al., 2001; Soriano et al., 2002; Pacher et al., 2002b; Veres et al., 2003; Lobo et al., 2005; DiPaola et al., 2005, Tatasargil et al., 2008; Horvath et al., 2008).

The role of PARP activation in the pathogenesis of critical illness was also extended into various other models, including hemorrhagic shock (Szabo, 1998b, Szabo et al., 1998a; Liaudet et al., 2000; McDonald et al., 1999; McDonald et al., 2000; Watts et al., 2001; Skarda et al., 2007), thermal injury (Avlan et al., 2005; Mota et al., 2008), polytrauma (St John et al., 1999), and into the acute dysfunction of various organs including lung (Liaudet et al., 2002; Murakami et al., 2004; Virag et al., 2004; Kiefmann et al., 2004; Mota et al., 2007; Pagano et al., 2007; Kim et al., 2008; Dhein et al., 2008; Vachetto et al., 2010; Lange et al., 2012; Hamahata et al., 2012), kidney (Martin et al., 2000; Chatterjee et al., 2003; Zheng et al., 2005; Devalaraja-Narashima et al., 2005; Tasatarhil et al., 2008; Szoleczky et al., 2012) and pancreas (Mota et al., 2005; Mazzon et al., 2006) where pharmacological PARP inhibition (e.g. PJ34, INH_2BP, INO-1001) and/or genetic PARP1 deletion demonstrated significant benefits in terms of improvement in organ function and prolongation of survival rate. For instance, both pharmacological inhibition of PARP and genetic deletion of PARP provides significant protection against the shock-associated increases in circulating blood urea nitrogen and creatinine levels in various forms of shock (Jagtap et al., 2002; McDonald et al., 2000). Similarly, the acute respiratory distress syndrome and lung dysfunction associated with circulatory shock of various etiologies is markedly attenuated by PARP inhibition or PARP deficiency (Liaudet et al., 2002, Shimoda et al 2003). Moreover, there is a significant protection by PARP inhibition against the shock-induced intestinal epithelial permeability (Cuzzocrea et al., 1997; Szabo et al., 1997b; Kennedy et al., 1998, Liaudet et al., 2000b; Liaudet et al., 2002). PARP inhibition downregulates the production of multiple pro-inflammatory mediators and attenuates the tissue infiltration of inflammatory cells (Szabo et al., 1997c; Szabo et al., 1997d; Cuzzocrea et al., 1998c; Szabo et al., 1998b). Similar protective effect of PARP inhibitors has been reported in splanchnic occlusion shock models (Cuzzocrea et al., 1997; DiPaola et al., 2005). Finally, the endotoxin- or sepsis-induced depression of the myocardial contractility is dependent on PARP activation (Pacher et al., 2002b; Goldfarb et al., 2002).

Although study guidelines comparable to the field of stroke (see above) have not been proposed in the field of circulatory shock, many of the aspects relevant to stroke also apply to shock, such as the need for establishing the therapeutic window, and the need for using clinically relevant models with multiple outcome variables. With respect to the former goal, multiple studies have demonstrated that the window of therapeutic intervention with PARP inhibitors in circulatory shock is significant: for example, post-treatment with PJ34 remained effective both in rodent and porcine models of circulatory shock (Jagtap et al., 2002; Goldfarb et al., 2002).

As far as clinically relevant models, in the field of critical illness, this is best achieved by using large animal models (porcine, canine or ovine). In one of the first such studies, the beneficial effects of PJ34 in bacterial sepsis were also confirmed in a model of sepsis induced by live *E. coli* sponge implantation in pigs: pharmacological inhibition of PARP provides marked hemodynamic improvements and a massive survival benefit (Goldfarb et al., 2002). In additional, PARP inhibitors of various structural classes have been tested in clinically-relevant models of ovine septic shock, Acute respiratory distress syndrome (ARDS) and burn injury. The results confirmed and extended the findings of the rodent studies and demonstrated that (1) significant PARP activation occurs in various organs, as well as in circulating leukocytes during circulatory shock (2) the degree of PARP activation is predictive of mortality and (3) pharmacological PARP inhibitors attenuate hemodynamic dysfunction, reduce organ failure and improve survival (Albertini et al., 2000; Shimoda et

al., 2003; Ivanyi et al., 2003; Murakami et al., 2004; Hauser et al., 2006; Maier et al., 2007; Asmussen et al., 2011; Bartha et al., 2011b; Lange et al., 2012; Hamahata et al., 2012).

Thus, from a preclinical standpoint, the evidence demonstrating the pathogenic role of PARP in critical illness, and the therapeutic potential of PARP inhibitors appears to be rather convincing. The efficacy is supported in multiple models: rodents as well as large animals, shock models utilizing bacterial components as well as live bacteria, pre-treatment as well as post-treatment, multiple modes of therapeutic action including protection from vascular dysfunction, multiple organ failure and overwhelming pro-inflammatory responses. The protection afforded by PARP inhibitors does not come at an expense of interfering with anti-bacterial defenses or exacerbating bacterial burden (Soriano et al., 2002; Murakami et al., 2004).

An interesting early study, demonstrating that the serum of septic patients impairs mitochondrial function *in vitro* in a manner that is dependent on PARP activation (Boulos et al., 2003) began to open the door for clinical translational work. The next remaining question is whether PARP activation occurs in human septic shock, and whether it correlates with disease severity or with outcomes. One such study, analyzing the potential role of PARP cardiac alterations in septic patients, was published in 2006 (Soriano et al., 2006). In this study, a total of 25 patients were enrolled. During the 28 days of follow-up, 12 patients died (48%). All patients were mechanically ventilated and received catecholamines. The two groups had similar APACHE II Scores. Cardiac enzymes, echocardiography analysis, cardiac output, vascular resistance did not show any significant difference at any time point during the study. Analysis of the patients' systemic inflammatory response was conducted by measuring plasma levels of C-reactive protein (CRP). In the first day, the CRP levels were similar in the two groups studied. However, on Day 3 the survivors presented a decrease in CRP, while the non-survivors maintained elevated CRP plasma levels. Clinical heart damage was assessed by plasma troponin, which showed a significant difference in the first day of study: the levels in the survivor group were 0.5 ng/ml, while those in the non-survivor group were 2.3 ng/ml ($p<0.05$). Data on Day 3 showed a persistent difference, in troponin serum levels between survivors and non-survivor group. There was a significant degree of cardiac dysfunction in the patients, as detected by left ventricular stroke work index. Non-survivors presented a more severe degree of cardiac depression, compared to survivors. The difference on stroke work data became more apparent from Day 3 to 6. End-diastolic volume from the left ventricle was obtained using data from pulmonary catheter and echocardiography. Using left ventricle size and ejection fraction from echocardiography and systolic volume from pulmonary catheter data, left ventricular end-diastolic volume was calculated. These data showed that the surviving septic patients presented an increase in end-diastolic volume, while non-survivors did not present with this pattern. There were no differences in catecholamine requirements in the surviving and nonsurviving groups. Histological myocardial damage, as assessed by hematoxylineosin staining, conducted in the hearts of the non-surviving patients, demonstrated an increased number of inflammatory cells in the heart tissue (Soriano et al., 2006). The study provided convincing evidence of nuclear staining for poly(ADP-ribose), the product of activated PARP, in the nuclei of the myocytes from septic patients, as well as in tissue-infiltrating mononuclear cells. There was a strong correlation between the poly(ADP-ribose) staining densitometry and troponin I and a similar, highly significant correlation between poly(ADP-ribose) staining densitometry and left ventricular stroke work index (Soriano et al., 2006).

A second study utilizing human specimens investigated the relationship between PARP activation and severe burn injury in a pediatric patient population (Olah et al., 2011). The results showed that PARP becomes activated in the skeletal muscle tissue immediately in response to burns, with the peak of the activation occurring in the middle stage of the

disease (2 weeks after burns). Even at the late stage of the disease (2-12 months after burn), an elevated degree of PARP activation persisted in some of the patients. Immunohistochemical studies localized the staining of poly(ADP-ribose) primarily to vascular endothelial cells and to mononuclear cells. Importantly, there same study also reported that there is a marked suppression of PARP activation in the skeletal muscle biopsies of patients who receive propranolol treatment as part of their therapy (Olah et al., 2011). The mechanism of this suppression is unclear; it may either be a specific regulatory effect via beta-adrenergic signaling, or, alternatively, it may be the result of an overall decrease in oxidative burden in the propranolol-treated patient population.

In conclusion, the observational clinical data coupled with the preclinical studies in rodent and large animal models, implicate PARP activation as a final common effector in multiple forms of critical illness. In our opinion, circulatory shock (together with stroke) encompasses a disease indication where all of the preclinical and translational components are available to support progression into clinical trials with PARP inhibitors. Just like in stroke, in sepsis, the survival outcome is poor and the therapeutic options are extremely limited. Just like in sepsis, the duration of the therapy would be expected to be relatively short, and the route of administration can be intravenous. And, finally, just like in stroke, the road of sepsis is “littered” with “corpses” in the form of multiple failed clinical trials, which markedly reduces the appetite of a typical pharmaceutical company for any future activity in the area of circulatory shock.

2.5. PARP inhibition for myocardial infarction

The first demonstration for the role of PARP in myocardial infarction occurred over 15 years ago, when Zingarelli discovered that PARP is activated in the reperfused myocardium, and, using a first-generation PARP inhibitor 3-AB, showed that inhibition of PARP reduces the size of the infarct (Zingarelli et al., 1997). 3-AB significantly improved the outcome of myocardial dysfunction, as evidenced by a reduction in creatine phosphokinase levels, diminished infarct size, and preserved the ATP pools (Zingarelli et al., 1997). These findings were subsequently confirmed and extended into various other models using PARP inhibitors of increasing selectivity and potency (Thiemermann et al., 1997; Bowes et al., 1998a; Bowes et al., 1998b; Docherty et al., 1999; Liaudet et al., 2001a, Liaudet et al., 2001b, Faro et al., 2002; Zingarelli et al., 2003; Khan et al., 2003; Kaplan et al., 2005; Song et al., 2008; Eltze et al., 2008; Roesner et al., 2010; Zhang et al., 2012). Furthermore, Zingarelli also demonstrated that PARP deficient mice are protected against myocardial reperfusion injury (Zingarelli et al., 1998; Yang et al., 2000). Likewise, hearts from PARP deficient mice are resistant to global ischemia-induced myocardial depression (Grupp et al., 1999, Pieper et al., 2000; Zhou et al., 2006; Yamazaki et al., 2011). The phenomenon can also be modeled *in vitro*: oxidant-treated cardiac myocytes exhibit PARP activation and reduction in cellular viability; this response is attenuated by PARP inhibitors (Gilad et al., 1997; Bowes et al., 1998a; Chen et al., 2004; Gero et al., 2007; Oh et al., 2009).

The time course of myocardial PARP activation is rather prolonged: it is present at 2 h after the start of reperfusion, and continues to be present as late as 24h after reperfusion. This delayed pattern of PARP activation is likely related to the continuing presence of free radical and oxidant production in the reperfused myocardium. The interpretation of these findings is that a massive, continuously occurring DNA single strand breakage (e.g. as the result of a continuous, on-going oxidative/nitrosative stress), which remains unrepaired for prolonged periods of time, is responsible for the prolonged pattern of PARP activation. The site of the most pronounced PARP activation is the area of necrosis and peri-infarct zone (i.e. area at risk). Most of the poly(ADP-ribose) staining occurs in cardiac myocytes and endothelial cells, indicating that the heart tissue and the vasculature themselves are the main sites of PARP activation (Liaudet et al., 2001a; Liaudet et al., 2001b; Zhang et al., 2012). In

addition, PARP activation also occurs in circulating mononuclear cells (Murthy et al., 2004; Toth-Zsamboki et al., 2006).

In addition to rodent models of regional ischemia-reperfusion (typically elicited by occlusion/re-opening of the left anterior descending coronary artery), the cardioprotective action of PARP inhibitors has been evaluated in other rodent models, PARP inhibitors have also been tested in various models of cardiac transplantation. In these models, too, the efficacy of PARP inhibition proved substantial, as evidenced by improved contractility of the transplanted hearts, and by increased survival time of the transplanted heart (Szabo et al., 2002a; Fiorillo et al., 2002; Liu et al., 2004; Szabo et al., 2005; Farivar et al., 2005; Szabo et al., 2006a; Szabo et al., 2006b; Gao et al., 2007). In addition to rodent models, the cardioprotective effect of PARP inhibition has also been demonstrated in various large animal models. Even in post-treatment models, where PARP inhibition does not affect the infarct size, PARP inhibitors have been shown to elicit improvements in cardiac contractility in a porcine model (Roesner et al., 2010), possibly due to improved energetic status of the reperfused heart (Docherty et al., 1999).

Taken together, the above data provide strong preclinical evidence for the role of PARP activation, and the therapeutic potential of PARP inhibitors in myocardial infarction. The therapeutic efficacy is sustained across multiple animal species (rodent and large animal), exhibits a good therapeutic window, and extends into multiple relevant outcome variables (infarct size, cardiac enzymes, contractility, inflammatory mediators, mononuclear cell infiltration into the heart and activation of circulating leukocytes). There are also multiple lines of human data showing PARP activation in the heart in various cardiac diseases (or diseases with cardiac involvement) including acute myocardial infarction and revascularization, where PARP activation has been demonstrated in circulating leukocytes (Toth-Zsamboki et al., 2006, Yao et al., 2008), cardiopulmonary bypass (Ramlawi et al., 2006) as well as septic shock (Soriano et al., 2006), aortic valve stenosis (Nagy et al., 2012), diabetic cardiomyopathy and chronic heart failure (Pillai et al., 2005a; Pillai et al., 2005b; Molnar et al., 2006). Taken together, the data are in support of further exploration of this indication for the clinical development of PARP inhibitors. In an early-stage clinical study in this direction Morrow and colleagues have assessed the effect of INO-1001 in 40 patients with ST-elevated myocardial infarction, undergoing percutaneous coronary revascularization (Morrow et al., 2010). Although the study was not statistically powered to test for clinical efficacy, the compound was well tolerated, and serial C-reactive protein and IL-6 levels showed a trend toward blunting of inflammation with INO-1001 (Morrow et al., 2010). These studies should provide impetus for additional clinical testing of PARP inhibitors in acute cardiac indications.

2.6. Indirect or non-specific approaches for preventing PARP activation

In addition to direct enzymatic inhibitors of PARP, there are a number of theoretical and practical ways to indirect inhibition of PARP activation, either by preventing the generation of reactive oxygen or nitrogen species that lead to DNA strand breakage (and, thereby activation of PARP), or by utilizing “non-specific” or indirect inhibitors of PARP. From the long list of such inhibitors - which include various xanthines, purines, vitamin D and a number of other compounds (e.g. Virag and Szabo, 2001; Szabo et al., 2006c; Mabley et al., 2007; Weseler et al., 2009) - in the following section we are highlighting those two areas, which, in our view have the highest translational relevance.

2.6.1. Inhibition of reactive oxygen or nitrogen species formation—Agents that suppress the induction of iNOS, such as TNF-α antibodies, IL-1β antibodies, glucocorticoids (Szabo et al., 1993; Szabo et al., 1994; Szabo and Thiemermann, 1994; Linn et al., 1997), or

direct inhibitors of nitric oxide synthase (Saunders et al., 2011), or various neutralizers of superoxide or peroxynitrite (Southan et al., 1996; Cuzzocrea et al., 1997b; Cuzzocrea et al., 1998a; Cuzzocrea et al., 1998b; Panas et al., 1998; Soejima et al., 2001; Szabo et al., 2002b; Obrosova et al., 2005; Lange et al., 2011) all have the potential of indirectly preventing PARP activation, as demonstrated in multiple preclinical studies.

One particular antioxidant worthy of some discussion is α-lipoic acid, a multifunctional molecule, with a significant antioxidant component, that has been used, with success, in the therapy of diabetic complications (Tahrani et al., 2010; Goraca et al., 2011). PARP activation plays a key role in the pathogenesis of diabetic endothelial dysfunction (Garcia Soriano et al., 2001; Soriano et al., 2001; Szabo et al., 2002c; Du et al., 2003b; Crocker et al, 2005; Pacher et al., 2005b; Horvath et al., 2009a; Horvath et al., 2009b; Choi et al., 2012), cardiomyopathy (Pacher et al. 2002; Xiao et al., 2004), neuropathy (Obrosova et al., 2004; Li et al., 2004; Li et al., 2005; Drel et al., 2011), nephropathy (Minchenko et al., 2003; Szabo et al., 2006d; Shevalye et al., 2010), retinopathy (Zheng et al., 2004; Sugawara et al., 2004; Obrosova et al., 2005; Obrosova et al., 2006; Drel et al., 2009) and erectile dysfunction (Kendrici et al., 2005; Nangle et al., 2010; Li et al., 2012), and α-lipoic acid has been demonstrated in preclinical studies to inhibit diabetes-associated PARP overactivation (Ihnat et al., 2007). While in diabetes, clinical therapy with specific PARP inhibitors may be a long way away, a shorter-term, indirect approach may involve the clinical use of α-lipoic acid. Metformin, another clinically used antidiabetic agent, has also been demonstrated to suppress PARP activation, at least *in vitro* (Mahrouf-Yorgov et al., 2009).

Supplementation of the endogenous antioxidant and reducing agent hydrogen sulfide (H_2S) (Szabo, 2007; Wang, 2012) has also been demonstrated to be able to prevent the oxidant-mediated activation of PARP in various *in vitro* and *in vivo* experimental settings (Sodha et al., 2008; Suzuki et al., 2011; Xie et al., 2012).

The above-mentioned approaches, in some cases, may have advantages (in addition to inhibiting PARP, the neutralization of ROS and RNS may have independent, additional benefits). On the other hand, when using such compounds/approaches, it will be very hard, if not impossible, to dissect the relative contribution of PARP-dependent vs. PARP-independent effects to the observed biological responses. NOS inhibitors and various classes of catalytic antioxidants are at various stages of research or development, and such approaches, clearly, hold the opportunity for indirect prevention of PARP activation in various disease conditions.

2.6.2. Gender/estrogen—As already mentioned in section 2.3.1, the efficacy of PARP inhibitors in rodent models of stroke is preferentially observed in male animals. (Eliasson et al., 1997, Hagberg et al., 2004, McCullough et al., 2005; Liu et al., 2009; Yuan et al., 2009). In fact, in some studies, in females, PARP inhibition can even exacerbate the degree of damage in stroke (McCullough et al., 2005; Liu et al., 2011). PARP1 genetic deficiency produces significant protection in the total group of animals (males and females analyzed together), but males were more strongly protected in contrast to females. Separate experiments showed that, PARP1 was activated over 1-24 hours in both genders, but the decrease of brain NAD^+ level during early ischemia was seen only in males (Hagberg et al., 2004).

Similar observations were noted in rodent models of shock and inflammation (Mabley et al., 2005). The endotoxin-induced inflammatory and vascular responses are cooperatively regulated by gender and PARP. The production of the inflammatory mediator TNF-α, the endotoxin-induced mortality, and the development of endotoxin-induced endothelial dysfunction were all markedly attenuated in female mice (compared to male mice), and

these responses were reduced by PARP inhibitors in male, but not female, mice. In fact, PARP inhibition in male animals, provided comparable protection against a number of inflammatory/cardiovascular parameters investigated as female gender, but no combination effects of the two protective factors (female gender and PARP inhibition) were noted (Mabley et al., 2005). In a subsequent series of investigations, conducted in porcine models of thoracoabdominal aortic ischemia-reperfusion injury, the inhibition by PARP inhibitors against the cardiovascular collapse was only observed in male animals, but not in females (Hauser et al., 2006).

What, then, is responsible for this marked gender difference? In the context of neuroinjury, a potential explanation for these findings is that the genes of AIF, as well for several proteins involved in perinatal hypoxia ischemia that may be related to PARP1 are localized on the X chromosome and may, in addition to NAD^+, be differentially expressed in males and females (Du et al., 2004). Another potential mechanism may be an enhancement of caspase-3 and caspase-9 activation in stroke in females (but not males) (Liu et al., 2011); the underlying mechanism for this gender difference in caspase activation remains to be explored. In fact, it has been previously known that in adult rodents, females sustain less injury than males after experimental ischemia, and that this resistance acquired after puberty and depends on the estrous cycle and is lost after menopause in accordance with putative effect of sex steroids, especially estrogen (Payan and Conrad, 1977; Hurn and Macrae, 2000). According to most studies, estrogen does not appear to inhibit PARP activation in a direct manner. When one simply combines recombinant PARP and estrogen *in vitro*, the catalytic activity of PARP does not appear to be affected (Mabley et al., 2005). Similar studies revealed that PARP activity in peripheral blood mononuclear cells (PBMCs) was significantly higher in male mice compared to female mice. However in this study, estrogen supplementation in female mice caused a significant increase in PARP activity in their PBMCs but a decrease in liver PARP activity (Zaremba et al., 2011) Interestingly, these authors also noted a difference in PARP activity between male and female human subjects, PBMCs from women had significantly lower PARP activity than those from men. Furthermore, women <45 years old (pre-menopausal) generally had lower PARP activity than older women and men, but the sample size was not large enough to reach statistical significance (Zaremba et al, 2011). This was the first demonstration of the effect of gender on PARP activity in human subjects. An interesting *in vitro* interaction can be noted between PARP, estrogen and the DNA, and these interactions are further reinforced by the presence of estrogen (Mabley et al., 2005). A model of interaction has been proposed between PARP and estrogen receptor alpha, whereby a stable complex may sequester PARP to specific regions on the DNA making it difficult to for its zinc fingers to access and recognize DNA breakpoints (without which its activation would be inhibited). It has been hypothesized that this action may contribute to the observed effects of estrogen *in vivo* (Mabley et al., 2005), although a direct link remains to be demonstrated. An additional mode of action may be the antioxidant property of the female sex hormones, which can exert cytoprotective effects, sometimes already in surprisingly low concentrations (Kuohung et al., 2011). Interestingly, male sex hormones may also have an effect on PARP activity: PBMCs isolated from male mice showed a lower degree of PARP activity after castration, which was not further affected by estrogen supplementation (Zaremba et al., 2011). These observations led the authors to propose that androgens stimulated PARP activity in PBMCs in these animals, rather than estrogen inhibiting PARP activity. However, since they also observed a reduction in PARP activity in livers from estrogen-supplemented female mice the effect of sex hormones may be tissue-specific. In support of this hypothesis, stroke model studies in mice reveal that castration decreases PARP-1 mRNA in brain cortex and reduces infarct size, and dihydrotestosterone reverses this effect (Vagnerova et al 2010). Taken together, complex, and currently only partially understood regulation exists in laboratory animals between gender and PARP activation.

What is the applicability of this gender difference in PARP-dependent responses to clinical translation in humans? Clearly, PARP inhibitors are not always ineffective in female animals. For example in the nonobese diabetic mice (which develop autoimmune beta-cell loss and a disease that resembles Type I diabetes) PARP inhibition is of significant therapeutic benefit (Pacher et al., 2002; Suarez-Pinzon et al., 2003), perhaps indicative of a potential strain difference in this respect. Moreover, in a non-human primate model of stroke, the PARP inhibitor tested was effective irrespective of gender (Matsuura et al., 2011). Finally, PARP inhibitors are protective in female sheep subjected to shock or burn and smoke inhalation damage (Shimoda et al., 2003). Thus, the limit of the applicability of these findings needs to be established in future (clinical) studies.

3. Clinical utility of PARP inhibition: conclusion and future directions

PARP inhibitors have come a long way since the discovery of the 3-substituted benzamides. They have demonstrated the potential to inhibit DNA repair and increase the efficacy of IR, DNA methylating agents and topo I poisons in a variety of cell-based and animal models of human cancer in preclinical studies. Importantly they may exploit the molecular pathology of cancer by selectively enhancing TMZ activity against cells with MMR defects and, critically, are synthetically lethal in cells with HRR defects. Since these defects are found almost exclusively in cancers but not normal tissues, this represents a truly tumor-specific therapy. It is the potential for synthetic lethality that has largely driven the clinical studies and there have been some encouraging observations in patients with BRCA1 or BRCA2 mutations. Biomarkers are needed to identify the potentially large pool of patients with other defects in HRR that may benefit from PARP inhibitor therapy. Toxicities have been seen in many of the combination studies but proper attention must be paid to the pre-clinical data regarding both appropriate combinations, and the need for much lower doses and shorter schedules for chemosensitization compared with single agent therapy, if these are to be minimized. Radiotherapy combinations are only now being investigated clinically and these may prove a more promising avenue to follow. Finally, a more comprehensive and comparative characterization of the potency and *in vivo* efficacy of the various PARP inhibitors will be necessary: Based on the current body of literature, each study utilizes only a limited number of PARP inhibitors; thus, we do not have a good feeling for the comparative potency or efficacy of these agents (nor a comparison of their side effect profiles). We also fully expect that medicinal chemistry efforts will continue and will yield new, improved classes of PARP inhibitors, either targeting the NAD^+ binding site, or, alternatively, perhaps by modulating functional domains other than the catalytic domain (for instance, thereby modulating the interactions of PARP with other proteins).

As far as the clinical development of PARP inhibitors for non-oncological indications, the existing clinical data indicate that stroke, traumatic brain injury, circulatory shock and acute myocardial infarction are some of the indications where PARP activation has been demonstrated to contribute to tissue necrosis and inflammatory responses (Figure 3). For these indications the preclinical data with PARP inhibitors of various classes are overwhelmingly positive, and support further human (clinical) testing. These indications are ones where (a) the clinical outcomes are severe (b) the clinical (unmet need is substantial), (c) the available clinical options are limited, and (d) relatively short-term therapy with the PARP inhibitor (parenterally administered) would be sufficient. Such trials would need to proceed with consideration for therapeutic window; with the inclusion of appropriately chosen biomarkers/polymorphisms for the trials, selection of the most appropriate PARP inhibitor; and should incorporate the best possible clinical trial design (e.g. gender as a clinical variable). Although all of the above indications are generally considered as ‘difficult’ (some of them have been even termed as ‘graveyards’ of drug development), it is

hoped that the clinical success of the PARP inhibitors in oncological indications will facilitate the expansion of some of these compounds into other indications as well.

Beyond the acute indications, there are multiple lines of strong preclinical data to support the consideration of some chronic indications, which have poor clinical options and high mortality. For instance, although, in quantitative terms, fewer studies have investigated the role of PARP in chronic heart failure, this indication is worth considering in the current article, because chronic heart failure presents with 5-year survival rates that are comparable or worse than many forms of cancer, and the therapeutic options are severely limited. Hence, the risk-benefit considerations that are relevant for cancer may also be similarly pertinent for considering PARP inhibition as an experimental therapy of chronic heart failure, in light of multiple lines of preclinical (Pacher et al., 2002c; Pacher et al., 2004; Pacher et al., 2006; Pillai et al., 2005a; Pillai et al., 2005b; Pillai et al., 2006; Bartha et al., 2008; Bartha et al., 2009) and clinical (Pillai et al., 2005b; Molnar et al., 2006) data demonstrating the pathogenetic importance of PARP activation in this condition.

Asthma bronchiale is another indication where multiple lines of preclinical data show that PARP inhibition/PARP deficiency attenuates inflammatory responses and improves bronchial reactivity both in pre-treatment and in delayed therapeutic regimens (Virag et al., 2004; Suzuki et al., 2004; Naura et al., 2009; Havranek et al., 2010; Datta et al., 2011). However, the experimental therapy of chronic heart failure, asthma, or some of the other indications discussed in earlier sections (e.g. neuroinflammation, chronic neurodegeneration) would require an orally active PARP inhibitor, which is well tolerated in chronic (multi-year) therapeutic regimens. Moreover, in certain indications (e.g. asthma), the patient population (pediatric/young adult) would represent additional regulatory hurdles for the introduction of a new chemical entity, especially one with known effects on DNA repair processes. All in all, we believe that all things considered (preclinical efficacy in rodent and non-rodent species, severity of disease, duration and route of the inhibitors' administration, regulatory and clinical considerations) stroke/acute neurotrauma, circulatory shock and acute myocardial events can be viewed as the prime non-oncological indications for the future clinical development of PARP inhibitors.

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Abbreviations

i.v.	intravenous
TNBC	triple negative breast cancer
HGSOC	high grade serous ovarian cancer
GBM	glioblastoma multiforme

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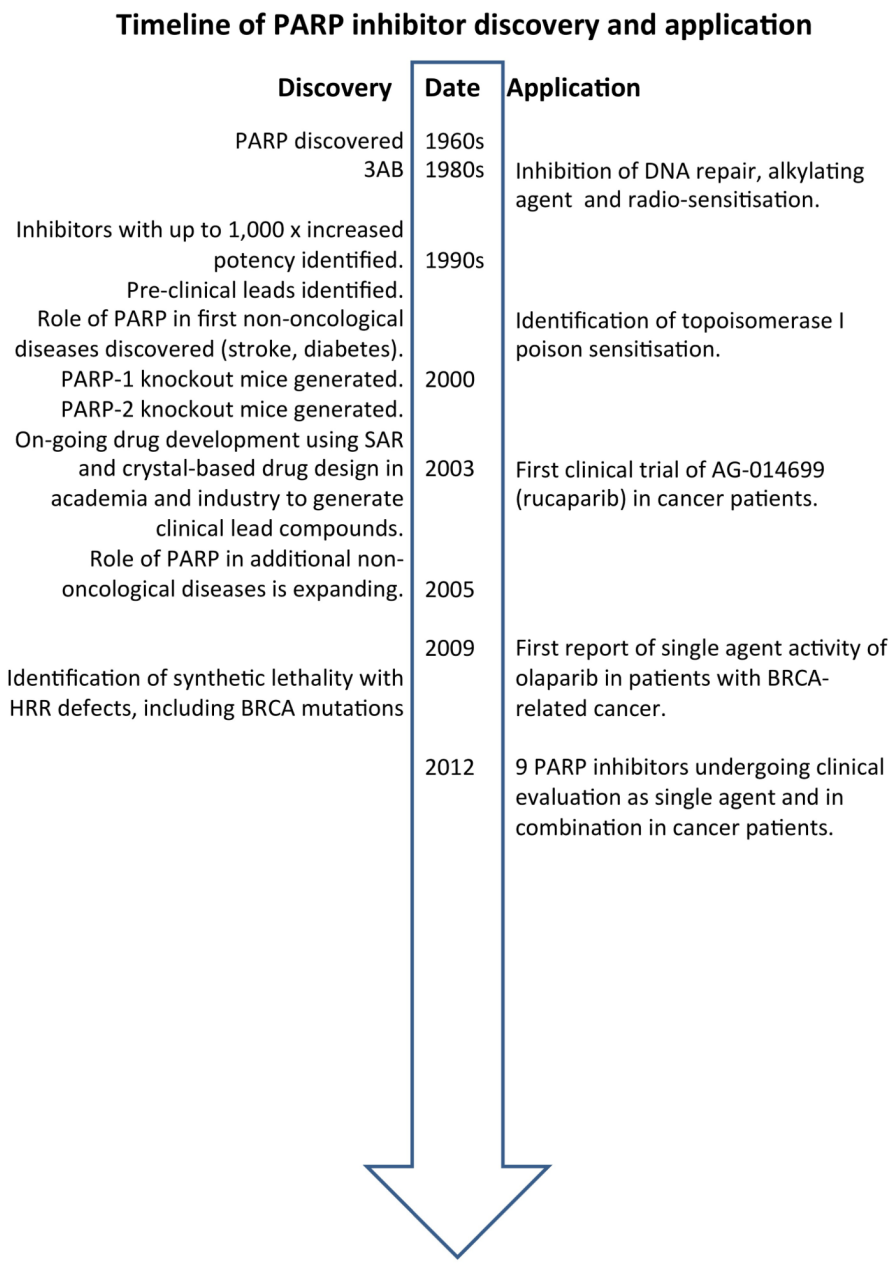


Figure 1. Timeline of PARP inhibitor discovery and application

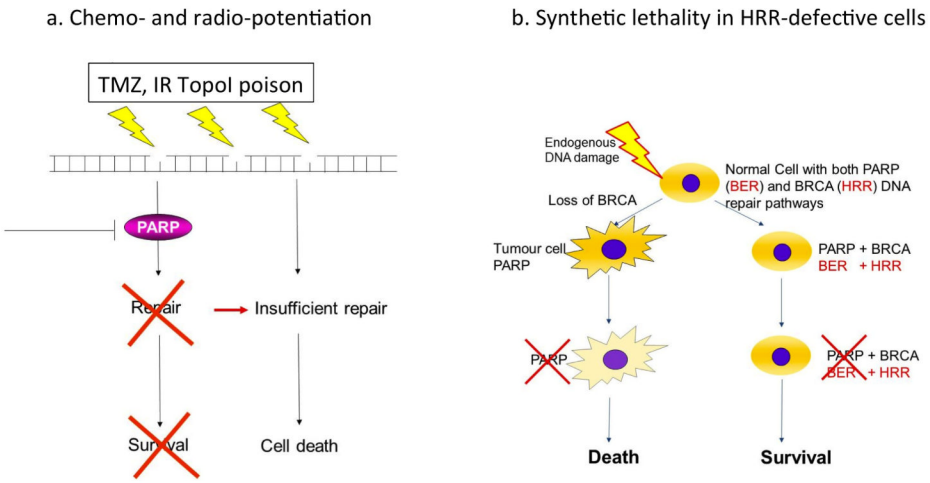


Figure 2. Mechanism of action of PARP inhibitors in cancer therapy

(a) PARP promotes the repair of DNA damage induced by IR, TMZ and topo I poisons allowing the cell to survive. If PARP is inhibited then repair is insufficient and DNA damage persists leading to cell death. **(b)** BER and HRR complement each other in the repair of endogenous DNA damage. Loss of BRCA1 or BRCA2 (or any other component of HRR) can lead to genomic instability and tumor development. Such tumor cells become more reliant on PARP for repair of endogenous DNA damage such that when PARP is inhibited the cell cannot repair its DNA sufficiently and dies. Normal cells that still retain functional HRR will survive even though PARP is inhibited.

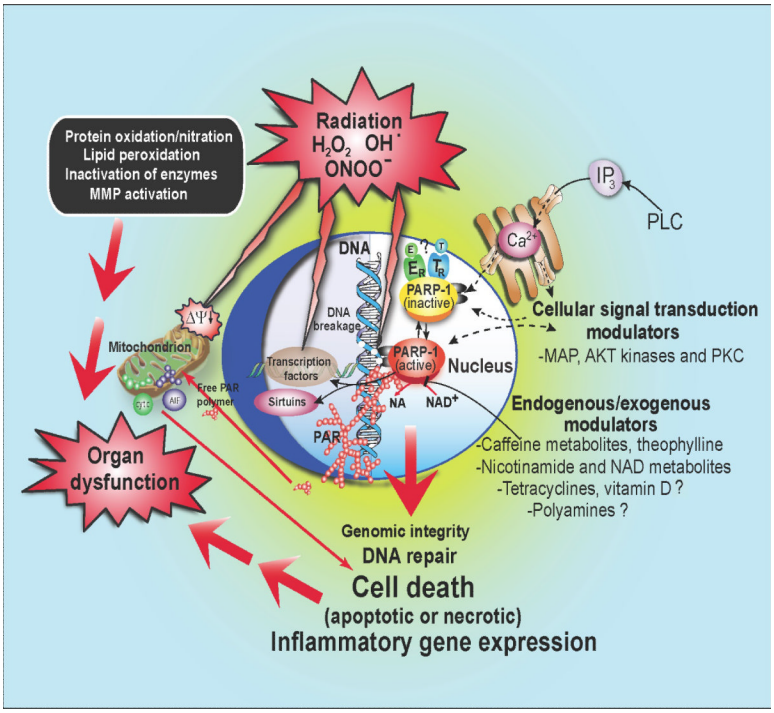


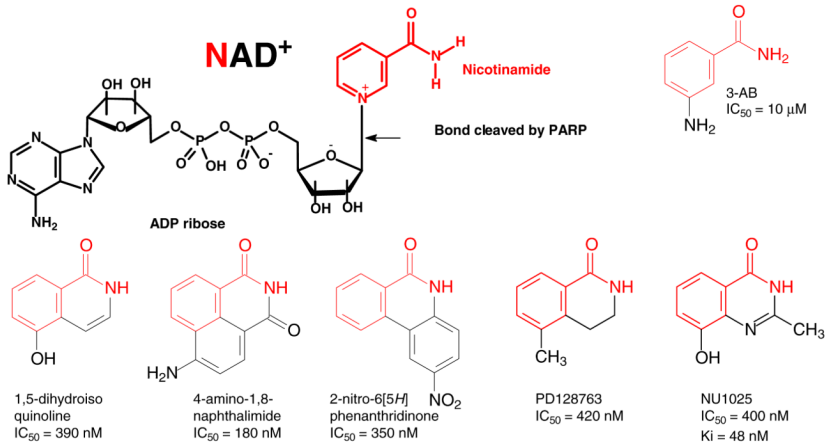
Figure 3. Pathogenetic role of PARP activation in various disease conditions characterized by oxidative/nitrosative stress, and regulation of PARP activation by various exogenous/ endogenous, regulators/modulators

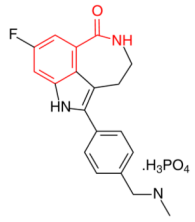
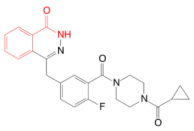
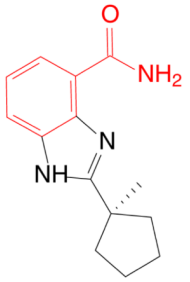
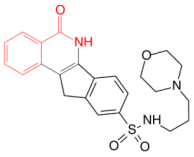
Under pathophysiological conditions (e.g. stroke, myocardial infarction, chronic heart failure, diabetes, circulatory shock, chronic inflammatory diseases, cancer, and neurodegenerative disorders etc.), nitric oxide and superoxide react to form peroxynitrite (ONOO) that induces cell damage via lipid peroxidation, inactivation of enzymes and other proteins by oxidation and nitration, and also activation of stress signaling, matrix metalloproteinases (MMPs) among others (Szabo et al., 2007; Pacher et al., 2007). Mitochondrial enzymes are particularly vulnerable to attacks by peroxynitrite, leading to reduced ATP formation and induction of mitochondrial permeability transition by opening of the permeability transition pore (PTP), which dissipates the mitochondrial membrane potential. These events result in cessation of electron transport and ATP formation, mitochondrial swelling, and permeabilization of the outer mitochondrial membrane, allowing the efflux of several proapoptotic molecules, including cytochrome *c* and apoptosis-inducing factor (AIF). In turn, cytochrome *c* and AIF activate a series of downstream effectors that mediate caspase-dependent and -independent apoptotic death pathways. In addition to its damaging effects on mitochondria, peroxynitrite, in concert with other oxidants, causes oxidative injury to DNA, resulting in DNA strand breakage which in turn activates the nuclear enzyme poly(ADP-ribose) polymerase (PARP1). Activated PARP1 consumes NAD^+ to build up poly(ADP-ribose) polymers (PAR), which are themselves rapidly metabolized by the activity of poly(ADP-ribose) glycohydrolase (PARG). Some free poly(ADP-ribose) may exit the nucleus and travel to the mitochondria, where they amplify the mitochondrial efflux of AIF (nuclear to mitochondria cross talk). Depending on the severity of the initial damage by peroxynitrite and other oxidants, the injured cell may either recover or die. In the latter case, the cell may be executed by apoptosis in case of moderate mitochondrial PTP opening and PARP1 activation with preservation of cellular ATP, or by necrosis in case of widespread permeability transition pore opening and PARP1 overactivation, leading to massive NAD^+ consumption and collapse of cellular ATP. Overactivated PARP1 also facilitates the expression of a variety of

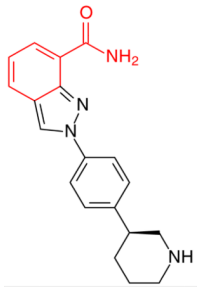
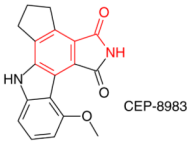
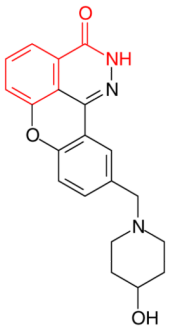
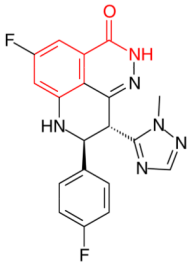
inflammatory genes leading to increased inflammation and associated tissue injury. Various endogenous factors can influence PARP activity either by forming a complex with PARP or inhibiting the binding of its substrate NAD^+ to the active site of the enzyme. Such examples may include estrogen (E), thyroid hormones (T), nicotinamide (NA), NAD^+ metabolites, and vitamin D. PARP activity can also be modulated by various kinases by phosphorylation (e.g., MAP kinases and PKC), and PARP can modulate kinase (e.g. AKT) activity. Different exogenous factors (e.g. caffeine and its endogenously formed metabolites, theophylline, and several other compounds may also inhibit PARP activity. Reproduced, with permission, from Pacher and Szabo, 2008.

Table 1

Clinical trials with PARP inhibitors in oncology indications.



PARP inhibitor structure (where available)	Company, date started	Single agent/ combination	Tumor type	Route, current stage (2012)
	AG-014699/ PF0367338 CO-338 **Rucaparib** Pfizer Now Clovis Oncology 2003	TMZ combination Various combinations Single agent	Solid tumors Melanoma Solid tumors BRCA mutant breast ovarian	I.V. Oral Phase II
	KU59436/ AZD2281 **Olaparib** AstraZeneca 2005	Single Agent Various Combinations	Solid tumors BRCA carriers TNBC/HGSOC Solid tumors	Oral Phase II
	ABT-888 **Veliparib** Abbott 2006	Single Agent Various Combinations	Various solid + Lymphoblastoid	Oral Phase II
	INO-1001 Inotek/ Genentech 2003/6	TMZ Combinations	Melanoma	I.V Phase I (terminated)

PARP inhibitor structure (where available)	Company, date started	Single agent/ combination	Tumor type	Route, current stage (2012)
	MK4827 Merck 2008	Single agent Combinations with TMZ or doxorubicin	Solid and hematological tumors GBM Ovarian	Oral Phase II Phase I
 CEP-8983	CEP-9722 (structure of this compound not available) Cephalon 2009	Single agent Combination with TMZ Gem/cis	Solid tumors lymphoma	Oral Phase I
	GPI21016/E7016 MGIPharma/ Eisai 2010	Combination with TMZ	Melanoma	Oral Phase II
	BMN-673 BioMarin 2011	Single agent	Various solid and hematological tumors	Oral Phase I

Notes: PARP cleaves NAD+, thereby releasing nicotinamide. All PARP inhibitors have the nicotinamide pharmacophore (highlighted in red). Early development of PARP inhibitors shown above the table, structures of those in clinical trial are embedded in the table.

Table 2

PARP activation and PARP-related polymorphisms in selected human diseases

Disease	Human evidence for PARP activation	PARP-related polymorphisms
Cancer	• In a panel of 19 human cancer cell lines, there was 3.5-fold difference in the PARP-1 expression level between the lowest and the highest expressors, with two neuroblastoma cell lines (NB 1691, SK-N-BE2C), two leukemia cell lines (Nalm6, PreB) and thyroid carcinoma cell line (ML-1) showing the highest expression levels (Zaremba et al., 2009). • PARP-1 expression was found to gradually increase in nonatypical and atypical endometrial hyperplasia compared with normal endometrial epithelium (Ghabreau et al., 2004). • PARP1 was found overexpressed in human breast cancers (Goncalves et al., 2011).	• Increased frequency of T2444C SNP in PARP1 correlates with higher risk of esophageal carcinoma, prostate cancer, melanoma and lung cancer (Hao et al, 2004; Lockett et al, 2004; Zhang et al, 2005; Li et al., 2006; Zhai et al., 2006; Zaremba et al., 2009). • Women carrying the PARP-1 Ala762Ala genotype are more susceptible to cervical carcinoma and to squamous cell carcinoma (Ye et al., 2012). • The presence of the PARP1 2819G allele is associated with an increased risk of gastric cancer (He et al., 2012). • rs3219125 in PARP1 is significantly associated with melanoma risk (Zhang et al., 2011). • The PARP1 Val762Ala and the PARP1 A762V SNP are associated with the risk of glioma development (Liu et al., 2009; Yosunkaya et al., 2010), with Non-Hodgkin lymphoma (Jin et al., 2010) and gastric cancer (Zhang et al., 2009). • Twenty rare genetic variants of PARP1 were detected in 11% of the cancers studied (Cao et al., 2007). • Polymorphisms in PARP1 gene are involved in interindividual differences in the response to platinum-based doublet chemotherapy in lung cancer (Shiraishi et al., 2010
Stroke	• Activation of PARP in brain sections from patients dying from stroke or brain ischemia due to cardiac arrest (Love et al., 1999; Love et al., 2000; Sairanen et al., 2009).	• No relevant polymorphisms were identified (Kato et al., 2000).
Neurotrauma	• Activation of PARP in brain sections from patients with brain trauma (Love et al., 1999; Love et al., 2000). • Evidence for PARylated proteins in the cerebrospinal fluid (Fink et al., 2008; Sarnaik et al., 2010).	• SNP rs3219119 of PARP1 is an independent predictor of favorable neurologic outcome in TBI (Sarnaik et al., 2010). • SNP rs2271347 of PARP1 correlates with the amount of PARylated proteins in the cerebrospinal fluid, but does not correlate with clinical outcomes (Sarnaik et al., 2010).
Myocardial infarction	• Increased PARP activation in circulating leukocytes in patients with myocardial infarction and therapeutic revascularization (Toth-Zsamboki et al., 2006; Yao et al., 2008). • A significant degree of PARP activation in the ischemic human myocardium, studied in right atrial appendage samples (Chowdhry et al., 2007).	• No published data on this subject.
Systemic inflammatory diseases	• Significant PARP activation in myocardial sections of patients with circulatory shock (Soriano et al., 2006). • In severe third-degree burns, PARP activation in circulating leukocytes and in microvascular endothelial cells (Olah et al., 2011).	• The −1082G > A alleles in the promoter region of the IL-10 gene physically interact with PARP1 in a manner that regulates IL-10 transcription (Kang et al., 2010). • In SLE, three IL-10 promoter SNPs (−1082A/G, −819T/C and −592A/C) are regulated by PARP1 in a similar manner (Chung et al., 2007).

Disease	Human evidence for PARP activation	PARP-related polymorphisms
Chronic heart failure	• Increased poly(ADP-ribosyl)ation in human heart samples in endstage heart failure (Pillai et al., 2005a; Pillai et al., 2005b; Molnar et al., 2006). • Increased poly(ADP-ribosyl)ation in human heart samples in heart failure followed by left ventricular heart assist device implantation (de Jonge et al., 2003).	• No published data on this subject.
Neuro-inflammatory diseases	• PARP activation and AIF nuclear translocation within apoptotic oligodendrocytes in the spinal cord of ALS patients (Kim et al., 2003). • PARP activation and AIF nuclear translocation in the CNS of human multiple sclerosis lesions (Veto et al., 2010).	• No published data on this subject.
Neuro-degenerative diseases	• Poly(ADP-ribosyl)ation in brain sections from patients with Alzheimer's disease, Parkinson's disease and ALS (Love et al., 1999; Soos et al., 2004; Kim et al., 2003; Kim et al., 2004).	• Haplotypes Ht3-TT and Ht4-CC of PARP1 are associated with an increased risk of Alzheimer's disease (Infante et al., 2007a; Liu et al., 2010). • Conflicting data in Parkinson's disease (Infante et al., 2007b; Brighina et al., 2011).
Local inflammatory diseases	• Auto-antibodies against PARP were demonstrated in rheumatoic arthritis, SLE and other autoimmune diseases. In addition, there is experimental evidence for increased poly(ADPribosyl) ation in biopsies from patients with colitis (Okolie et al., 1979; Negri et al., 1990; Rosen et al., 2004; Jeoung et al., 2004; Reumaux et al., 1995).	• Two relevant PARP1 haplotypes were detected in rheumatoid arthritis: haplotype A (410T-[A](10)-[CA](10-12)-1362C) and haplotype B (410C-[A](11)-[CA](13-20)-1362T); haplotype B is statistically overrepresented in the arthritic group (Pascual et al., 2003). • The SNPs -1963A --> G and +28077G --> A are associated with an increased risk of nephritis; one variant [+40329T --> C(V762A)] is associated with an increased risk of arthritis, while -1963A --> G SNP shows a protective effect on arthritis (Hur et al., 2006). • Val762Ala and Leu54Phe polymorphisms are associated with glomerulonephritis risk (Shestakov et al., 2007), but not for arthritis (Onaran et al., 2009). • Lack of association was noted between PARP polymorphisms and rheumatoid arthritis in a Korean population (Lee et al., 2012).
Vascular diseases including diabetic complications	• Activation of PARP has been observed in human atherosclerotic plaques, in microvessels and lymphocytes of 2 diabetic patients (Martinet et al., 2002; Szabo et al., 2002c; Shrikhande et al., 2006; Adaikalakoteswari et al., 2007) and in gestational diabetes (Horvath et al., 2009b). • Diabetes was found to increase PARP activation in the ischemic human myocardium, studied in right atrial appendage samples (Chowdhry et al., 2007).	• Leu54Phe and Val762Ala polymorphisms in PARP1 are associated with diabetic polyneuropathy development in diabetic patients (Nikitin et al., 2008). • Val762Ala polymorphism of PARP-1 is significantly more frequent in Type II diabetic patients subjects without coronary artery disease than those with coronary artery disease (Narne et al., 2012).
Organ transplantation	• Increased expression of PARP-1 was reported in transplanted kidneys. This response correlated with worsened outcome after transplantation (O'Valle et al., 2005; O'Valle et al., 2007).	• No published data on this subject.
Pulmonary diseases	• Increased poly(ADPribosyl)ation was reported in peripheral blood lymphocytes from patients with chronic obstructive pulmonary disease (Hageman et al., 2003).	• Val762Ala polymorphism in PARP1 is associated with lower asthma risk (Tezcan et al., 2009).