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Poly (ADP-ribose) polymerase (PARP) inhibitors approved for the treatment of cancer☆

Robert Roskoski Jr.

Blue Ridge Institute for Medical Research, 221 Haywood Knolls Drive, Hendersonville, NC 28791, United States

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ABSTRACT

The human PARP enzyme family contains 17 members that are divided into five subfamilies, the chief one of which includes the DNA-dependent enzymes (PARP1/2/3). These enzymes participate, *inter alia*, in DNA repair, transcription, chromatin remodeling, and cells cycle progression. PARP 1/2 catalyze both the mono-ADP ribosylation (MARylation) and poly-ADP ribosylation (PARylation) of its various substrates including itself. PARP1/2 catalyze the formation of large (200 units) linear and branched ADP-ribosyl polymer chains. When the PARP enzyme binds to DNA containing various lesions, it is activated. ADP ribosylated PARPs mark the sites of DNA damage and attract repair proteins. Back-of-the-envelope calculations suggest that the number of single-strand breaks and base loss or modification ranges from 10,000 to 100,000 per cell per day. To function properly, at least in proliferating and germline cells, the DNA lesions must be repaired. Otherwise, cell death may ensue or deleterious mutations that can cause cancer or cell senescence can occur. The FDA has approved four PARP inhibitors (olaparib, rucaparib, niraparib, and talazoparib) for the treatment of ovarian, breast, prostate, and pancreatic cancer. These agents are approved for cancers with homologous-recombination repair deficiencies including *BRCA1/2* mutations. These inhibitors are approved agents used for neoadjuvant, adjuvant, and maintenance therapies. The Chinese NMPA has approved three PARP antagonists (fuzuloparib, pamiparib, senaparib) for the treatment of ovarian cancer. All seven of these drugs are orally bioavailable and fall within the criteria of Lipinski's rule of five. Drug resistance develops in most PARP-inhibitor-treated cancer patients within one or two years.

1. Overview of the PARP family

The human PARP enzyme family contains 17 members [1–3]. They have been catalogued and grouped by their cellular roles and structures into five subfamilies including (i) DNA-dependent proteins (PARP1/2/3), (ii) tankyrases (PARP5a/5b/7), (iii) CCCH Zn finger proteins (PARP9/12/13), MacroDomain proteins (PARP4/6/8/14/15), and unclassified family members (PARP10/11/16) [4]. The MacroDomain typically consists of 130–190 amino acids that adopt a distinct fold consisting of a central β-sheet surrounded by 4–6 α-helices. PARP1, which is located in the cell nucleus and mitochondrion, catalyzes both the mono-ADP ribosylation (MARylation) and poly-ADP ribosylation (PARylation) of its various substrates including itself. It participates, *inter alia*, in DNA repair, transcription, chromatin structure modulation and modification, epigenetics, cells cycle progression, apoptosis, innate immunity, and cell stress responses. PARP2, which is

Abbreviations: AlogP, atom-based calculated Log P; AP, apurinic/apyrimidinic; ATM, Ataxia Telangiectasia Mutated; ATR, Ataxia Telangiectasia and RAD3-related; ART, ADP-ribosyl transferase; *BRCA*, breast cancer gene; CAT, catalytic domain; CDK, Cyclin-Dependent protein Kinase; CHK, CHeckpoint Kinase; cs, catalytic subunit; DDR, DNA damage repair; DSB, double strand break; FDA, the Food and Drug Administration of the United States; HD, helical domain; HER2, human epidermal growth factor receptor 2; HormR, hormone receptor; HRD, homologous recombination deficiency; HRR, homologous recombination repair; IgG, immunoglobulin; LE, ligand efficiency; LipE, lipophilic efficiency; NMPA, National Products Administration in China; NSCLC, non-small cell lung cancer; PARP, Poly ADP-ribose polymerase; PDL1, programmed death-ligand 1; P-gp, P-glycoprotein; PSA, polar surface area; Ro5, Lipinski's rule of five; SSB, single strand break; WGR, Trp-Gly-Arg; Zn, zinc finger.

☆ Chemical compounds studied in this article: Abiraterone (PubChem CID: 132971); Enzalutamide (PubChem CID: 15951529); Fuzuloparib (PubChem CID: 56649297); NAD^+ (PubChem CID: 10897651); Niraparib (PubChem CID: 24958200); Olaparib (PubChem CID: 23725625); Pamiparib (PubChem CID: 135565554); Rucaparib (PubChem CID: 9931954); Senaparib (PubChem CID: 68389008); Talazoparib (PubChem CID: 135565082)

E-mail address: rrj@brimr.org.

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located in the nucleus and cytoplasm (centrosome in G_0/G_1) catalyzes the poly-ADP ribosylation of its substrates with branching. It functions in DNA repair, chromatin structure modulation, and epigenetics. PARP3, which is located in the nucleus and cytoplasm (centrosome in G_0/G_1) catalyzes mono-ADP ribosylation of its substrates. It modulates DNA repair, participates in DNA damage surveillance, chromatin structure modulation, epigenetics, transcriptional regulation, and monitors mitotic fidelity. The other members of the PARP family participate in a variety of processes including DNA repair, innate immunity, intracellular vesicle trafficking, cell stress responses, cell motility, spindle pole regulation, cell replication, and membrane and nuclear envelope formation [3].

PARP1/2/3 and PARP5a/b catalyze the post-translational poly-ADP ribosylation of their protein substrates [3]. The other members, except for the catalytically impaired PARP9 and PARP13, catalyze the mono-ADP ribosylation of their targets. The ADP-ribose marker serves as a signaling moiety that is generated by the transferase activity of PARPs using NAD^+ as substrate. The ADP-ribose is usually linked to proteins; however, it can be attached to DNA, RNA, or other chemical entities. Aspartate, glutamate, lysine, and serine residues are the most common attachment sites of the polymers to proteins [4]. Other linkage residues include arginine and cysteine [3]. The main residues of PARP1 linked to poly (ADP-ribose) are D387, E488, E491, S499, S507, and S519. These sites are important for the auto-modification of PARP1 and are necessary for its function. Fig. 1 depicts the addition of the first ADP ribose to a protein-serine residue with NAD^+ as donor and the protein as acceptor and nicotinamide is the leaving group. PARP members 1, 2, 5a, and 5b catalyze the generation of large (200 units) polymer chains of ADP-ribose, but only PARP1/2 can generate branched polymers (Fig. 2). The newly formed branch structure is then extended linearly. The linear poly-ADP ribose is made up of serial α (1→2) glycosidic bonds linking two ribose units and the branches consist of a central ribose attached to two ribose moieties (Fig. 2) each of which extends its chain linearly. PARG – poly (ADP-ribose) glycohydrolase – catalyzes the hydrolytic removal of the ADP ribosyl units, allowing for their reutilization.

All members of the PARP family possess a catalytic C-terminal ADP-ribosyl domain containing about 350 amino acid residues [4]; however, this domain in PARP9 and PARP13 is nonfunctional. PARP1 has a molecular weight of 113 kDa and contains six domains (Zn1, Zn2, Zn3, BRCT, WGR, CAT) and PARP2 and PARP3 are considerably smaller (66 kDa and 60 kDa, respectively) and contain three domains (NTR, WGR, CAT). Zn refers to zinc fingers, BRCT is the BRCA carboxyterminal domain, WGR refers to Trp-Gly-Arg that characterizes the segment, and

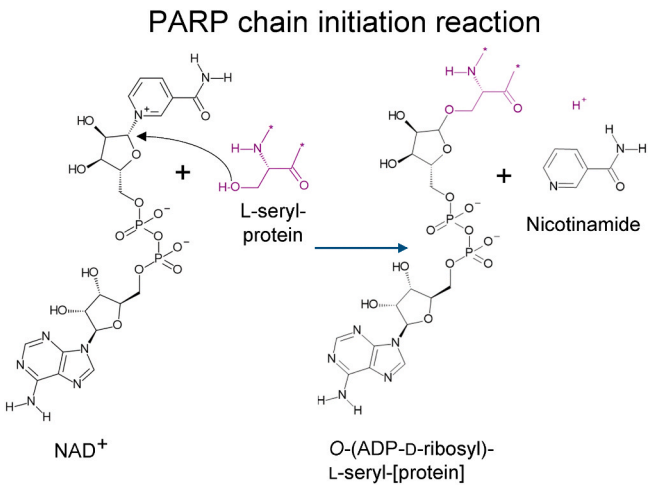

Fig. 1. PARP chain initiation reaction. In this post-translational PARylation reaction, the protein-serine hydroxyl group reacts with NAD^+ to produce an ADP-ribosylated derivative with nicotinamide as the leaving group. Adapted from https://www.uniprot.org/uniprotkb/P09874/entry.

CAT (the catalytic domain). BRCT domains denote the carboxyterminal region of the breast cancer tumor suppressor protein (BRCA1) and these domains occur in proteins participating in DNA repair. The CAT domain is composed of two portions: a regulatory HD or helical domain and ART or an ADP ribosyltransferase segment. NTR refers to the amino-terminal region. The zinc finger, WGR, and the BRCT domains interact with DNA [5]. PARP1 binding to intact DNA involves Zn1, Zn2, Zn3, and BRCT domains whereas binding to damaged DNA involves Zn1, Zn2, Zn3, and WGR. When PARP1 is bound to native DNA devoid of any lesions, the enzyme is catalytically inactive. When it binds to DNA containing various lesions, PARP1 is activated. The helical domain contains six α-helices and becomes unfolded by the abnormal DNA-induced allosteric activation mechanism that allows access to the NAD^+ binding site. The ART sub-domain is the functional enzymatic component that synthesizes poly (ADP-ribose) chains on itself and other proteins. It is the ADP ribosylated PARPs that mark the sites of DNA damage and attract repair proteins. The structures of these three proteins based upon AlphaFold PDB coordinates are depicted in Fig. 3.

The canonical His-Tyr-Glu (H-Y-E) triad (also known as the ADP-ribosyl transferase or ART signature) is essential for PARP catalysis [7]. H862 forms a hydrogen bond with the 2′-hydroxyl group of the NAD^+ adenine-ribose moiety. Y896 stacks with the nicotinamide ring through π-π interactions and E988 forms a hydrogen bond with the 2′-hydroxyl group of the nicotinamide ribose, which helps to properly position and polarize the NAD^+ molecule for the nucleophilic attack during catalysis. Other important catalytic residues include Y986 and M890. The former is part of the pyrophosphate attachment site of NAD^+ and the latter interacts with the adenine moiety of NAD^+ via hydrophobic interactions. G876 and R878 stabilize the adenine-ribose binding residues in the catalytic acceptor site. Note the wide distribution of these residues within the catalytic domain of PARP1 (Fig. 4A, the listed interactions are omitted for clarity). A schematic of the nucleophilic attack of the acceptor with the donor is depicted in Fig. 4B.

There are three potential mechanisms that PARP1 may use to attach poly ADP ribose to itself [7]. These include a unimolecular process as one molecule of PARP1 interacts with a DNA break, becomes catalytically active, and modifies itself (as a monomer). In this case one PARP1 enzyme serves as a catalyst and an acceptor of poly ADP-ribosylation at the same time. A second possible mechanism involves a bimolecular process involving *symmetric* homodimers of PARP1. A homodimer of two PARP1 molecules is formed by protein-protein interaction. The binding of the first molecule to the DNA lesion induces its interdomain rearrangement, resulting in both activation of this molecule and the symmetric self-assembly of the second PARP1 molecule driven by rearrangement of the protein-protein interface. The active PARP1 homodimer consists of two identical subunits, both simultaneously functioning as a catalyst and acceptor of the ADP-ribosyl moiety. A third potential mechanism involves a bimolecular process with *asymmetric* homodimers of two PARP1 molecules. A DNA-bound PARP1 subunit is active and functions only as a catalyst. The second PARP1 molecule is inactive and functions only as an acceptor of poly (ADP-ribose). In contrast, non-self post-translational ADP ribosylation involves a *heterodimer* of PARP1 and another target protein. The DNA-bound PARP1 molecule acts as a catalyst and mediates the addition of ADP ribosyl groups to non-PARP1 proteins. See Ref. [7] for a complete discussion of the above mechanisms and the mechanisms of poly (ADP-ribose) chain initiation, elongation, and branching.

2. DNA damage

Each human diploid cell contains 3×10^9 DNA bases within 26 chromosomes [8]. Enrico Fermi back-of-the-envelope calculations suggest that the number of single-strand breaks and base loss or modification is about 10,000 per cell per day [8]. Together with other types of damage, the number of daily DNA lesions may amount to 100,000. Moreover, a single session in the sun may produce up to 10^5

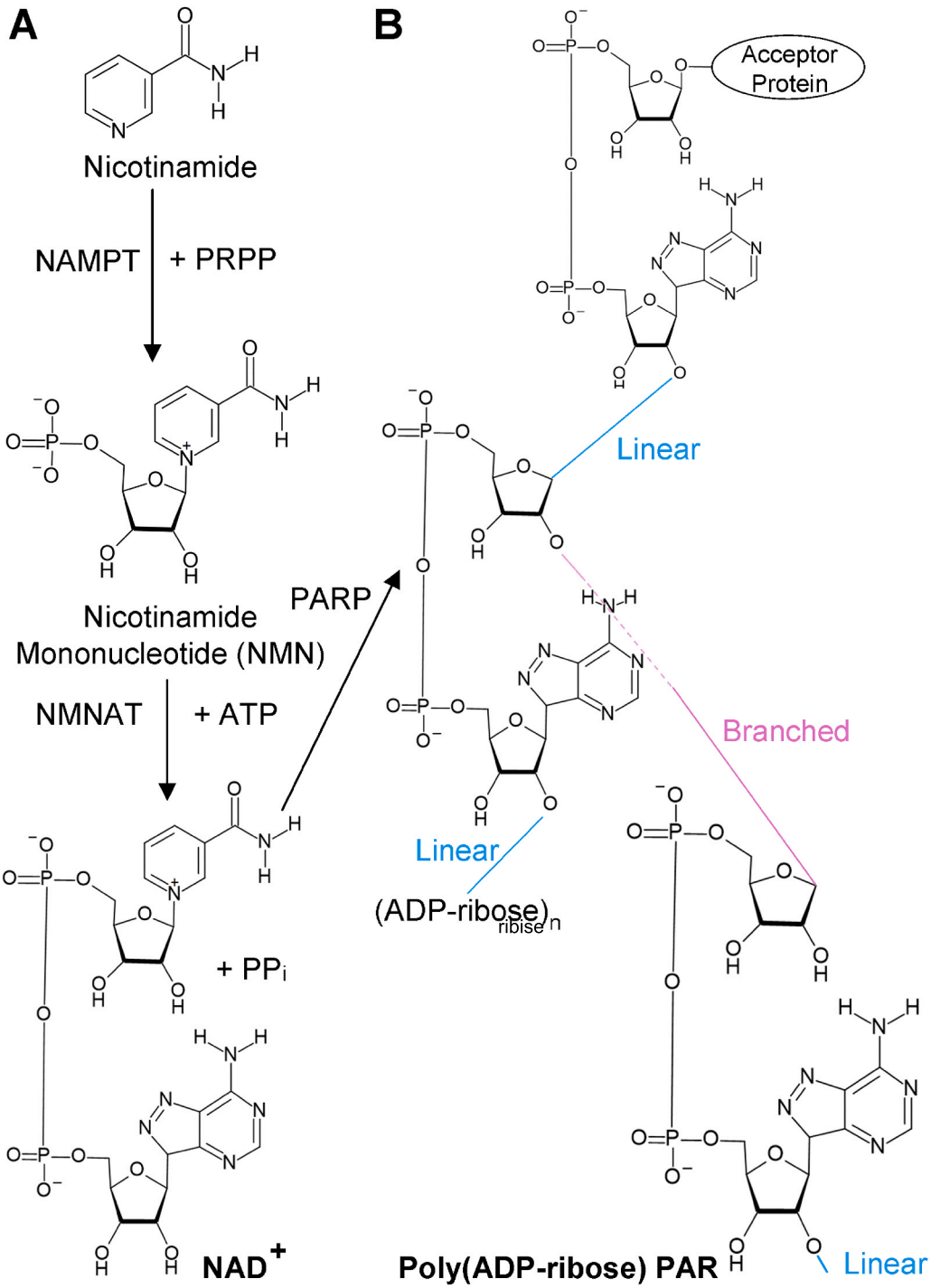

Fig. 2. (A) Biosynthesis of NAD^+. NAM, nicotinamide; NAMPT; nicotinamide phosphoribosyltransferase; PRPP, 5-phosphoribosyl-1-pyrophosphate; NMNAT, Nicotinamide adenylyltransferase; PP_i, pyrophosphate. (B) Biosynthesis of target-linked PAR from NAD^+. PARP, poly (ADP-ribose) polymerase. Poly (ADP-ribose) is elongated by the addition of ADP-ribosyl units in a linear (light blue) or branched (light purple) manner as catalyzed by PARP. Adapted from Ref. [2].

photoproducts in each skin cell. To function properly, at least in proliferating and germline cells, the DNA lesions must be repaired. Otherwise, cell death may ensue or deleterious mutations that can cause cancer or cell senescence can occur. While the absence or loss of individual DNA repair pathways is compatible with life, DNA repair processes are highly conserved and essential for cell survival. Nearly all DNA damage in a cell is rapidly repaired, usually in minutes. For this reason, humans and other organisms possess several mechanisms to protect against DNA damage with many of them involving the participation of PARP enzymes.

The mechanisms for producing DNA damage include both intrinsic properties of life in an aqueous-oxygen milieu and extrinsic factors such as tobacco smoke and ultraviolet and ionizing radiation [9]. Alkylation of DNA is both mutagenic and cytotoxic. Alkylating agents can arise intrinsically from oxidative damage or from cellular methylation donors such as S-adenosyl methionine or extrinsically from components in tobacco smoke. Most mutagenic alkylation products are O^6-alkylguanines and O^4-alkylthymines. During replication, the former base-pair with thymine instead of cytosine leading to G > A transition mutations and the latter base pairs with guanines instead of adenine leading to T > C

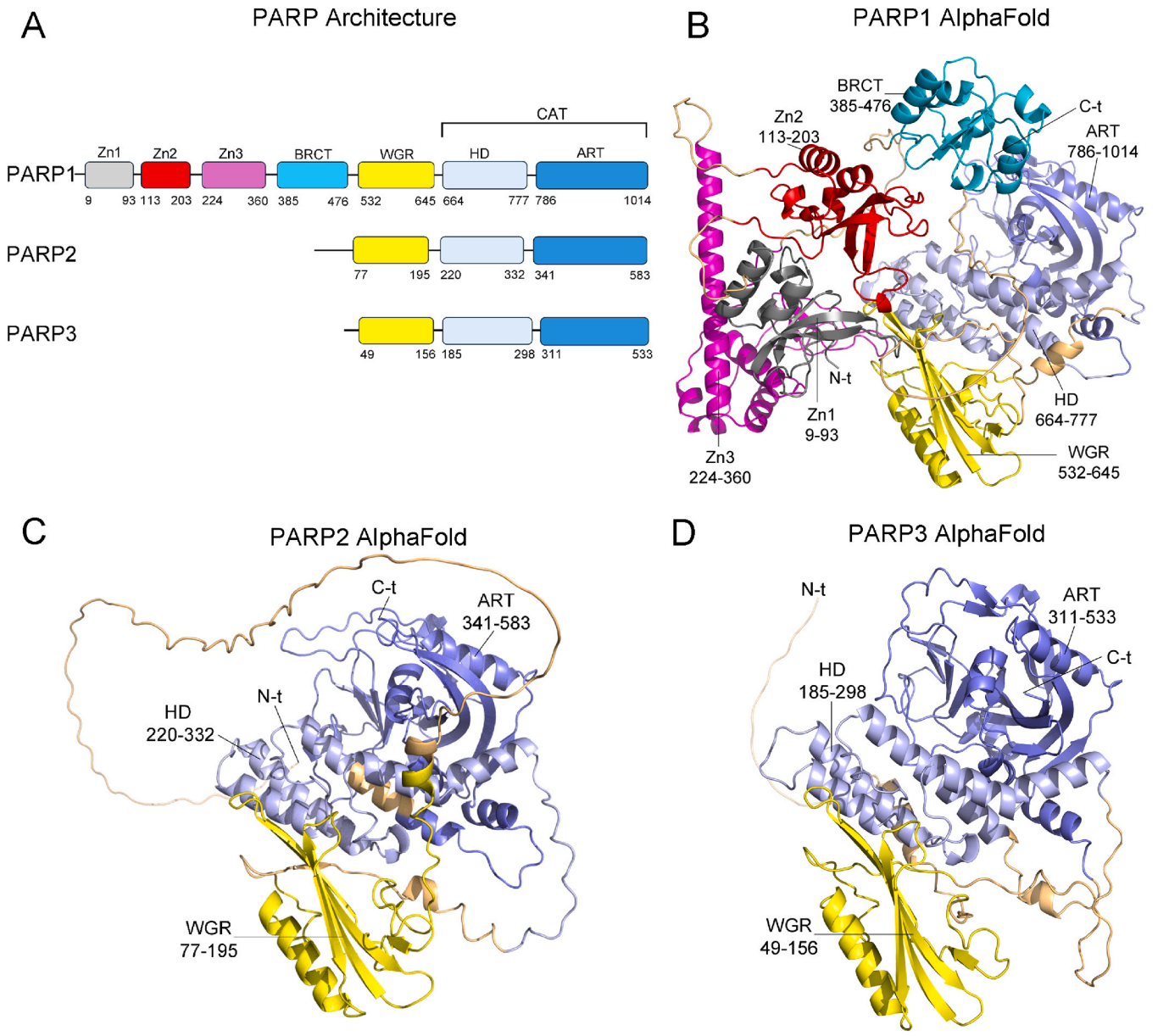

Fig. 3. (A) PARP components. Zinc fingers 1/2/3; BRCT is a domain first described by its location on the BRCA1 C-terminus; WGR, refers to the tryptophan (W)-glycine (G)-arginine (R) domain, HD is a helical domain and ART is the ADP ribosyl transferase domain. The domain numbering system was taken from Ref. [6]. (B) A cartoon of PARP1 based upon AlphaFold coordinates. (C) PARP2 structure based upon AlphaFold coordinates. (D) PARP3 structure based upon AlphaFold coordinates. The WGR segment is depicted in yellow, the HRD segment is light blue, and the ART component is dark blue. C-t, carboxy-terminus; N-t, amino-terminus.

mutations.

Ultraviolet radiation such as occurs in sunlight generates various photoproducts including cyclobutene pyrimidine dimers that pose as an obstacle to DNA and RNA polymerases [9]. Ionizing radiation from α-particles (He nuclei), β-particles (electrons), γ-rays, and X-rays produce double-strand breaks (DSBs). Radiation also generates reactive oxygen species (ROS) producing apurinic/apyrimidinic (AP) sites. Cigarette smoke and ethanol (which yields reactive acetaldehyde via the alcohol dehydrogenase reaction) are exogenous agents that form covalent linkages with DNA. Ionizing radiation, ultraviolet radiation, and chemotherapeutic agents such as cisplatin, carboplatin, and cyclophosphamide can produce DNA-DNA or DNA-protein crosslinked adducts. Such lesions disrupt DNA replication, transcription, and recombination.

Reactive oxygen species include the superoxide anion radical ($O_2^{\bullet-}$), the very reactive hydroxyl radical (•OH), ozone (O_3), and hydrogen peroxide (H_2O_2) [9]. These agents have the potential to modify DNA bases. Guanine is particularly susceptible to oxidation yielding 8-oxo-7, 8-dihydroguanine, the *syn* conformation of which incorrectly base pairs with adenine via non-Watson-Crick Hoogsteen base pairing. Other base modification reactions produce hypoxanthine, xanthine, and uracil. These result from the hydrolytic deamination of adenine, guanine, and cytosine, respectively.

DNA base mismatches occur owing to errors in DNA replication, base modification, or radiation [9,10]. Errors during DNA replication occur when a noncomplementary base is incorporated, leading to a mismatch with the template strand. While DNA polymerases have a proofreading function, this function is not perfect and errors can occur. DNA bases can spontaneously change into a different tautomeric structure and pair with an incorrect base thereby leading to a mismatch. During homologous recombination, heteroduplex formation can occur with strands of DNA from two homologous DNA strands with different sequences resulting in a product with mismatched base pairing.

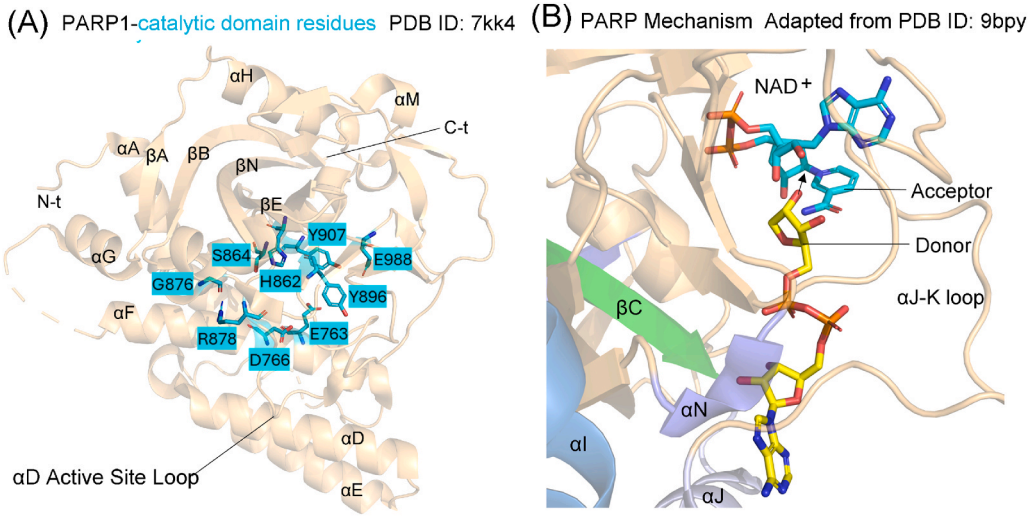

Fig. 4. (A) Important structural and catalytic residues occurring in PARP1. (B) The PARP mechanism illustrating the nucleophilic attack of the donor ADP-ribosyl group with NAD^+, the acceptor. The carbon atoms of the donor are colored yellow and those of the acceptor are cyan.

Other types of DNA damage include single strand breaks (SSBs) and double strand breaks (DSBs) [9,11]. SSBs commonly result from the oxidation of deoxyribose. Oxygen oxidizes deoxyribose in DNA primarily through the action of the hydroxyl radical. The hydroxyl radical abstracts a hydrogen atom from the deoxyribose sugar, creating a reactive deoxyribose radical. This radical then reacts with oxygen to form a peroxyl radical (ROO•), which leads to DNA strand breaks and modified nucleosides, such as 5′-aldehyde or 5′-carboxylate products. DSBs are generated by ionizing radiation and chemotherapeutic agents such as carboplatin and radiomimetic drugs such as phleomycin and bleomycin. DSBs can occur at the same location, or the lesions may be 10–20 base pairs apart. DSBs can cause inversions, deletions, and chromosomal translocations leading to genetic disorders and possibly cancer.

Repairing damaged DNA is necessary for the maintenance of physiological transcription, replication, survival, and genomic stability [6]. Most DNA damage occurs on just one DNA strand and is catalogued as a single strand break (SSB). These lesions are generally easy to repair owing to the availability of the complementary strand acting as a template. Single strand breaks include nicks (bases are intact but the DNA backbone is broken), gaps (absence of a nucleotide), or abasic AP sites (apurinic/apyrimidinic). Sukhanova et al. reported that PARP1 binds most strongly to nicks followed by lessor affinity for nucleotide break sites and then AP sites [12]. Double-stranded breaks are more difficult to repair and are dependent on the stage of the cell cycle and the presence or absence of a template [6]. If there is an available DNA strand template, repair is accomplished by homologous recombination (HR). HR occurs primarily during the S and G_2 phases of the cell cycle using sister chromatids as a template for error-free repair. Key proteins in homologous recombination include RAD51, which forms filaments for strand invasion, and RAD52, which acts as a mediator. Other important proteins include RAD54 for DNA remodeling, BRCA1 and BRCA2, which stabilize RAD51 and process DNA breaks, and the MRN (Mre11, RAD50, Nbs1) composite, which initiates signaling at double-strand breaks. Lacking a template, repair occurs by nonhomologous end joining (NHEJ) which directly ligates broken ends. The Ku70/Ku80 protein composite binds to the broken ends, recruits other factors like the DNA-dependent protein kinase catalytic subunit (DNA-PKcs), and the ends are processed and ligated by DNA ligase IV. DNA-PKcs is a large protein with a molecular weight of 469 kDa when compared with PKAcs with a molecular weight of 40 kDa. NHEJ is the predominant pathway during the G_0 and G_1 stages of the cell cycle.

ATM, ATR, CHK1/2, RAD51, and WEE participate in the DNA repair response [13]. Ataxia Telangiectasia Mutated (ATM) is a protein-serine/threonine kinase that activates checkpoint signaling at double strand breaks (DSBs) caused by genotoxic stresses such as ionizing ultraviolet light (UV). This kinase mediates the phosphorylation of MDC1 (mediator of DNA damage checkpoint protein 1), histone H2AX, protein-serine/threonine kinase CHK2, and p53, all involved in cell cycle regulatory checkpoints and DNA repair. Ataxia Telangiectasia and RAD3-related kinase (ATR) is a protein-serine/threonine kinase that activates checkpoint signaling upon genotoxic stresses such as ionizing radiation (IR), ultraviolet light (UV), or DNA replication stalling, thereby acting as a DNA damage sensor. Its substrates include p53, CHK1, BRCA1, the BLM ATP-dependent helicase (RecQ-like DNA helicase BLM), PrimPol (the DNA initiating primase and the DNA elongation polymerase that bypass replication-stalling lesions) and PALB2 (Partner and localizer of BRCA2).

CHK1 is a protein-serine/threonine kinase that is required for checkpoint-mediated cell cycle arrest and activation of DNA repair in response to the presence of DNA damage or unreplicated DNA [13]. CHK2 is a protein-serine/threonine kinase that is required for checkpoint-mediated cell cycle arrest, activation of DNA repair, and apoptosis in response to the presence of DNA double-strand breaks. RAD51 is an ATP-dependent protein that plays an important role in homologous strand exchange, a crucial component of DNA repair through homologous recombination (HR). WEE1 is a protein-tyrosine kinase that catalyzes the phosphorylation and inactivation of cyclin B1-complexed CDK1; it reaches a maximum activity during the G_2 phase of the cell cycle and a minimum as cells enter the M phase. WEE2 is a protein-tyrosine kinase that catalyzes the phosphorylation and inhibition of CDK1 (cyclin-dependent protein kinase) and acts as a key regulator of meiosis during both prophase I and metaphase II. The large number of proteins involved in the DNA damage response indicates its complexity and reflects the biological importance of maintaining genome integrity.

To minimize genotoxicity, PARP molecules swiftly locate damaged DNA within a nucleus containing abundant (100 mg/ml) intact DNA [6]. The concentration of DNA base pairs corresponding to 100 mg/ml is 75,000 μM and the back of the envelop estimated concentration of nuclear PARP1 is 15 μM corresponding to a ratio of 5000:1. On average, each PARP molecule scans 5000 base pairs thereby facilitating the rapid identification of DNA lesions. PARP1 uses an intersegment transfer mode to increase the rate of DNA damage surveillance and recognition [6,14]. The zinc finger segments bind tightly to DNA while the WGR portion binds with lower affinity. The release of PARP1 from the initial

site is facilitated by the WGR-domain binding to an additional DNA molecule. When the stronger zinc finger domains dissociate from DNA, the WGR-domain acts like an arm and initiates movement by gripping onto a new segment of DNA that promotes a 'monkey bar' mechanism or intersegment transfer. PARP1 scans the genome by swinging from one DNA location to another, the way a child grabs onto monkey bars.

3. PARP inhibitors

3.1. Therapeutic indications of the PARP inhibitors

The US FDA has approved four PARP inhibitors for the treatment of ovarian, breast, prostate, and pancreatic cancer (Table 1) [15–17]. The estimated number of new cases of ovarian cancer in the US in 2025 is 21,000 and the number of deaths is estimated at 13,000 [18]. The corresponding numbers for breast cancer are 320,000 and 43,000, those for prostate cancer are 314,000 and 36,000, and those for pancreatic cancer are 67,000 and 52,000, respectively. Breast cancer is the most common cancer diagnosed in women. It ranks second for cancer deaths in women, surpassed only by lung cancer. Ovarian cancer is the eighth most common cancer in women, but it is the fifth leading cause of cancer death for women. Prostate cancer is the second most frequently diagnosed cancer in men after lung cancer. It is the most common cancer in men, accounting for about 30 % of all new cancer cases in males in 2025. Pancreatic cancer is the 10th most common cancer in the United States and carries a high mortality rate.

Ovarian, tubal, or peritoneal cancers are serious conditions exhibiting little improvement in the 5-year survival rate over the past three decades [19]. Current standard of care includes primary cytoreductive surgery followed by platinum-based chemotherapy (with or without bevacizumab) or neoadjuvant chemotherapy (pre-surgical therapy used to minimize the size of the tumor) followed by cytoreductive surgery and further postoperative adjuvant chemotherapy (with or without bevacizumab). These approaches, while effective in achieving initial disease control, fail to prevent recurrence in most patients. The introduction of poly (ADP-ribose) polymerase inhibitors (PARP inhibitors) has improved the treatment landscape and management of these malignancies in patients with high-grade serous BRCA-variant and homologous recombination-deficient (HRD) advanced-stage tumors by targeting DNA repair. About 10 % of breast cancer patients have *BRCA1/2* mutations [20]. PARP inhibitors are now established as standard maintenance therapy after first-line treatment of recurrent platinum-sensitive disease. Clinical studies have shown that PARP blockers are effective in treating patients with platinum-sensitive ovarian cancer [21]. However, the long-term benefits and risks associated with PARP inhibitors are under study.

The combination of PARP inhibition and *BRCA1/2* mutations are synthetic lethal, which describes a situation in which the action of the drug combined with that of the *BRCA1/2* gene product together result in cell death, but inhibition by the drug or the presence of a *BRCA1/2* mutation does not [22,23]. Owing to synthetic lethality, defects in BRCA1/2 render cells vulnerable to PARP antagonists resulting in cell

Table 1
US FDA approved orally available PARP blockers [a].

Generic (Brand Name) Company	FDA approval year	Ovarian cancer	Breast cancer	Prostate cancer	Pancreatic cancer	Removed indications
Olaparib (Lynparza) AstraZeneca	2014	Maintenance treatment of *BRCA*-mutated advanced ovarian cancer, HRD-positive advanced ovarian cancer with bevacizumab, and treatment of recurrent cancer	Adjuvant treatment in HER2-negative high-risk early breast cancer harboring *gBRCA* mutations, HER2-negative metastatic breast cancer harboring *gBRCA* mutations	Metastatic castration-resistant prostate cancer (i) harboring HRR mutations and (ii) with abiraterone and prednisone or prednisolone in patients with *BRCA*-mutations	Maintenance treatment of metastatic pancreatic adenocarcinoma harboring *gBRCA* mutations	Treatment of advanced ovarian cancer after three or more prior lines of chemotherapy harboring *gBRCA* mutations
Rucaparib (Rubraca) Clovis	2016	Maintenance treatment of recurrent ovarian cancer harboring *BRCA* mutations who are in a complete or partial response to platinum-based chemotherapy.		Metastatic castration-resistance prostate cancer harboring *BRCA* mutations who have been treated with a taxane-based chemotherapy and androgen receptor-directed therapy		Treatment of ovarian cancer harboring *BRCA* mutations after two or more prior lines of chemotherapy
Niraparib (Zejula) GlaxoSmithKline	2017	Maintenance treatment of advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with either a *BRCA* mutation and/or genomic instability				Treatment of advanced HRD-positive ovarian cancer after three or more prior lines of chemotherapy
Talazoparib (Talzenna) Pfizer	2018		Treatment of germline *BRCA*-mutated (g*BRCA*m) HER2-negative locally advanced or metastatic breast cancer	Treatment of HRR gene-mutated metastatic castration-resistant prostate cancer (mCRPC) in combination with enzalutamide		

[a] *BRCA,* breast cancer gene; *gBRCA,* germline breast cancer gene; HER2, human epidermal growth factor receptor 2; HRD, homologous recombination deficiency; HRR, homologous recombination repair.

death, a desired outcome. The specific mechanisms of action of PARP inhibitors are intricate. Besides blocking PARP polymerase activity, the formation and trapping of PARP-DNA complexes at single strand breakpoints prevent DNA repair, leading to additional formation and accumulation of lethal double strand breaks. PARP trapping is a mechanism where the PARP molecule is trapped on the DNA, which interferes with the ability of the cell to replicate. The relative effectiveness of the FDA approved PARP blockers to form trapped olaparib:rucaparib:niraparib:talazoparib complexes is 1:1:2:100, indicating that talazoparib is by far more efficacious than the other agents. [24].

Surgery and radiation are the mainstay therapies for early-stage and metastatic breast cancer [25]. HER2 (human epidermal growth factor receptor 2), HormR (hormone receptor), ER (estrogen receptor), and PR (progesterone receptor) status play a significant role in planning treatment. Immunohistochemical markers (ER, PR, HER2), proliferation marker protein Ki-67, and immunomarkers (tumor-infiltrating lymphocytes and PDL1) are also used in planning treatment. Patients with *BRCA1/2* mutations, which occur in about 10 % of breast cancer patients [13,20] are candidates for PARP inhibitor therapy. Patients without these mutations that are HormR-positive/HER2-negative (about two-thirds of patients) are candidates for endocrine-based therapy with estrogen-receptor modulators (raloxifene, tamoxifen, toremifene), estrogen-receptor degraders (elacestrant, fulvestrant), and aromatase inhibitors (anastrozole, letrozole, exemestane) [24]. A variety of cytotoxic chemotherapeutic agents are used to treat HormR-negative breast cancer patients including taxanes (docetaxel, paclitaxel), anthracyclines (doxorubicin, epirubicin), antimetabolites (capecitabine, gemcitabine, fluorouracil, methotrexate), alkylating agents (carboplatin, cisplatin, and cyclophosphamide), and drugs that target microtubules (eribulin, ixabepilone, ado-trastuzumab emtansine) [26]. Additional standard first-line and follow-up therapy options include targeted approaches such as CDK4/6 inhibitors, phosphatidylinositol-3 kinase (PI3K) inhibitors, and anti-PDL1 immunotherapy, depending on the tumor type and molecular profile.

Like breast cancer, early-stage prostate cancer is treated with surgery and radiation therapy [27]. Prostate cancer is also treated with androgen receptor antagonists like enzalutamide, apalutamide, darolutamide, bicalutamide and flutamide, and androgen synthesis inhibitors like abiraterone. Charles Brenton Huggins, who was a urologist at of the University of Chicago, was awarded the Nobel Prize in 1966 "for his discoveries concerning hormonal treatment of prostate cancer." His initial work was published in the early 1940s and the procedure used for androgen depletion was orchiectomy [28]. His first-treated patient died two decades later from a myocardial infarction. Once prostate cancers metastasize, they may be lethal without treatment (one can die from prostate cancer or with prostate cancer) [27]. Moreover, late-stage prostate cancers become resistant to chemotherapy and hormone therapy. PARP inhibitors are a targeted therapeutic modality that is used in the late-stage treatment of selected prostate cancers. They play a crucial role in treating metastatic prostate cancer that is not responding to hormone therapy, so-called castration-resistant prostate cancer. The goal of targeted therapy is to kill cancer cells without harming healthy cells. PARP inhibitors block DNA damage repair proteins leading to cell death. They work best on prostate cancers that have mutations in DNA damage repair genes. About 8–16 % of men with late-stage, castration-resistant prostate cancer have these mutations. The most common of these gene mutations involves *BRCA2* with an incidence of 3–5 % [29]. They hinder DNA damage repair responses. The *BRCA2* mutations alone increase the risk for prostate cancer and promote metastases. Men with the *BRCA2* gene mutation are five times more likely to be diagnosed with prostate cancer than those without it.

About 10–15 % of newly diagnosed pancreatic cancer patients present with early-stage disease, about 25–30 % present with regional disease, and 50–60 % have distant metastases at the time of diagnosis, factors that contribute to the poor prognosis associated with this malignancy [30]. Surgery is used in the management of localized disease, and its safety and efficacy have improved in recent years owing to the increased use of minimally invasive laparoscopic surgical techniques. Furthermore, systematic chemotherapy prolongs survival. Neoadjuvant chemotherapy and adjuvant chemotherapy (post-surgery) are both used for the management of pancreatic cancer. Radiation therapy is occasionally used in the treatment of pancreatic cancer, but its efficacy is unclear.

Targeted therapies have been introduced based on genetic testing in metastatic pancreatic cancer and have shown promising results after first-line therapies fail [30]. These targeted therapies include the larotrectinib, entrectinib, and repotrectinib protein kinase blockers for NTRK-mutated cancers; the dabrafenib and trametinib protein kinase inhibitors for cancers with a $BRAF^{V600E}$ mutation; the selpercatinib kinase blocker for cancers with *RET* gene fusions; pembrolizumab (Keytruda) – the monoclonal antibody immune checkpoint inhibitor that blocks the PDL1 protein on T-cells – for high microsatellite instability (MSI-high), mismatch repair gene-deficient (dMMR), or high-tumor-mutation-burden (TMB) cancers; and fam-trastuzumab deruxtecan for cancers with an overexpression of HER2. However, only 1–2 % of pancreatic cancers exhibit MSI-high/dMMR, and the presence of other mutations is also very low. In contrast, about 85 % of pancreatic cancers possess $KRAS^{G12D}$ mutations. The two FDA-approved KRas blockers (adagrasib, sotorasib) target the cysteine in $KRas^{G12C}$, but not the aspartate in $KRas^{G12D}$. About 5–9 % of patients with pancreatic cancer have germline or somatic mutations in the *BRCA1* or *BRCA2* gene, and these patients are candidates for the use of PARP inhibitors. To conclude, pancreatic cancer is a disease with poor long-term survival; however, recent developments in pharmacotherapy have changed its treatment and have modestly better outcomes with improved survival.

3.2. PARP inhibitor properties

3.2.1. Olaparib

Olaparib is an orally bioavailable fluorophenyl-phthalazine derivative (Fig. 5A) that is FDA approved for the treatment of ovarian, breast, prostate, and pancreatic cancers (Table 1). Olaparib was the initial PARP inhibitor that received FDA approval (2014), notably for patients with ovarian cancer with germline *BRCA* mutations who had completed at least three chemotherapy regimens. The drug has IC_{50} values of 5 nM and 1 nM for PARP1 and PARP2, respectively [31]. The drug is nestled in a PARP1 cleft that interacts with the nicotinamide group of NAD^+ and it extends into the catalytic acceptor site. The carbonyl oxygen of the drug forms a hydrogen bond with the hydroxyl group of S904 and the N–H group of G863; the N–H group from the phthalazine ring forms a hydrogen bond with the carbonyl oxygen of G863, and the N–H group of Y896 forms a hydrogen bond with a drug carbonyl group (Fig. 6A). Y908 interacts with olaparib via π-π interactions and D766, H862, A880, and F897 interact hydrophobically with the drug.

See Ref. [32] for a summary of the clinical trials that led to olaparib's FDA approval in 2014 for the use as monotherapy in patients with harmful or suspected deleterious germline *BRCA*-mutated (as detected by an FDA-approved test) advanced ovarian cancer treated with three or more prior lines of chemotherapy. The drug was also approved in the European Union for the maintenance treatment of patients with platinum-sensitive, relapsed, *BRCA* mutation-positive (germline and/or somatic), high-grade, serous epithelial ovarian, fallopian tube or primary peritoneal cancers who are in partial or complete response to platinum-based chemotherapy. Common adverse reactions (≥20 %) associated with olaparib include anemia, fatigue, nausea, vomiting, abdominal pain, dysgeusia (unpleasant taste in the mouth), constipation, decreased appetite, diarrhea, thrombocytopenia, and dyspnea; anemia and fatigue are the most troublesome side effects and managed with dose modification [17].

3.2.2. Rucaparib

Rucaparib is an orally effective 1,3,4,5-tetrahydro-6H-azepino

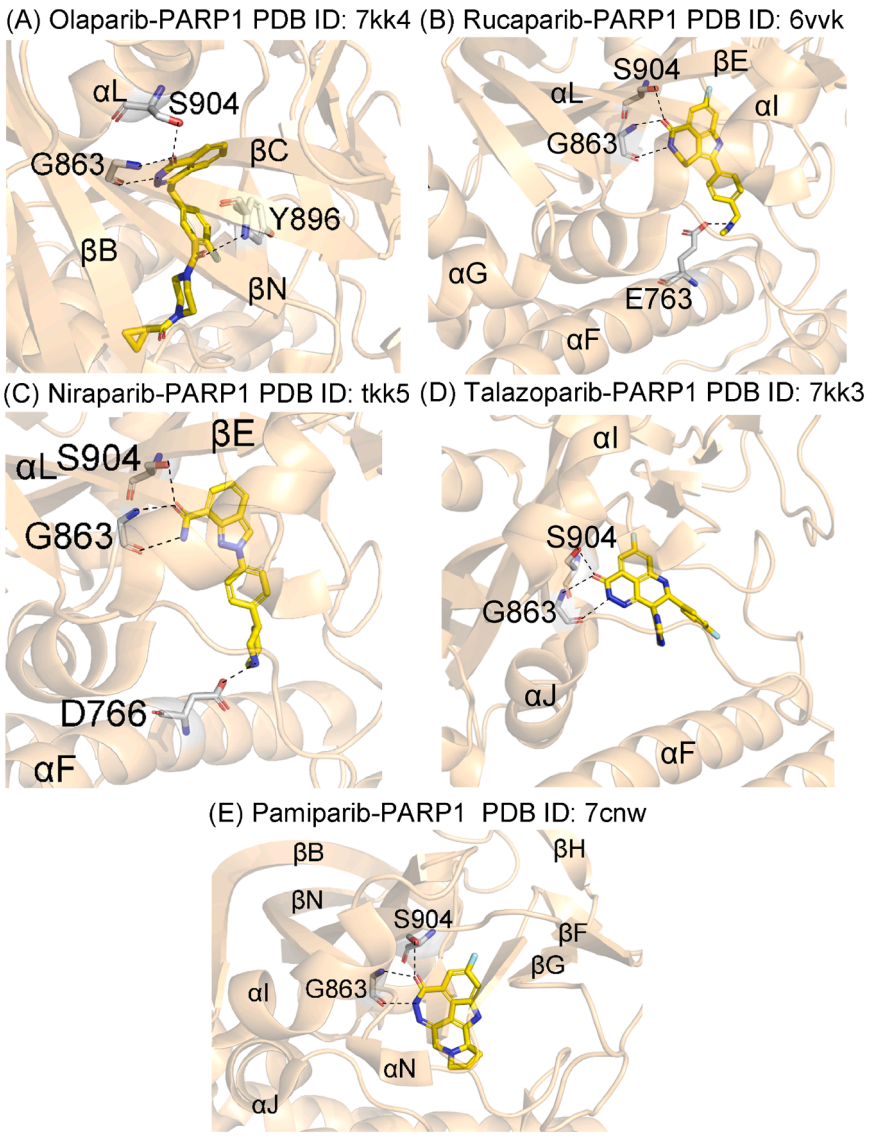

Fig. 5. Selected Drug-PARP1 complexes. The carbon atoms of the drug are yellow and those of the PARP1 amino acid residues are gray. The dashed lines indicate polar bonds.

(5,4,3-cd) indol-6-one derivative (Fig. 5B) that is FDA approved for the treatment of ovarian and prostate cancer (Table 1). It was granted accelerated FDA approval in 2016 for the treatment of patients with *BRCA* mutations who had undergone at least two chemotherapy regimens. The drug has an inhibitory IC_{50} value of 1.4 nM versus PARP1 [31]. The carbonyl oxygen of the drug forms a hydrogen bond with the hydroxyl group of S904 and the N–H group of G863; the N–H group from the indole ring forms a hydrogen bond with the carbonyl oxygen of G863, and the terminal N–H group of the drug hydrogen bonds with the terminus of E763 (Fig. 6B). A898 and K903 make van der Waals contact with rucaparib and H862, G888, Y889, Y896, Y907 interact hydrophobically with the drug.

See Ref. [33] for a summary of the clinical trials that led to the FDA accelerated approval of rucaparib (Rubraca; Clovis Oncology, Inc.) for the treatment of patients with *BRCA* mutation-positive (germline and/or somatic) advanced ovarian cancer who had been treated with two or more chemotherapies. Common adverse reactions (≥ 10 %) among patients with ovarian cancer were fatigue, nausea, vomiting, diarrhea, decreased appetite, dysgeusia, dyspnea, dizziness, dyspepsia, photosensitivity reactions, increased blood creatinine, and hematological toxicities (anemia, leukopenia, neutropenia, thrombocytopenia) [17]. These adverse events are treated with dose adjustments and targeted symptom management.

3.2.3. *Niraparib*

Niraparib is an orally effective indazole-7-carboxamide derivative (Fig. 5C) that is FDA approved for the treatment of ovarian cancer patients who have a complete or partial response to platinum-base therapy and whose cancer is associated with homologous recombination

deficiency (HRD) (Table 1). The drug has IC_{50} values of 3.8 nM and 2.1 nM for PARP1 and PARP2, respectively [31]. The carboxamide moiety hydrogen bonds with S904 and G863 and the piperidine N–H group forms a hydrogen bond with the R-group of D766 (Fig. 6C). Niraparib makes van der Waals contact with Q759 and H862; the drug interacts hydrophobically with V762, Y889, Y896, F897, A898, K903, and Y907.

See Ref. [34] for a summary of the clinical trials that led to the FDA approval of niraparib for the maintenance treatment of recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancers who have responded to platinum-based chemotherapy. Common adverse reactions (incidence ≥10 %) in patients who received niraparib were nausea, vomiting, diarrhea, fatigue, constipation, musculoskeletal pain,

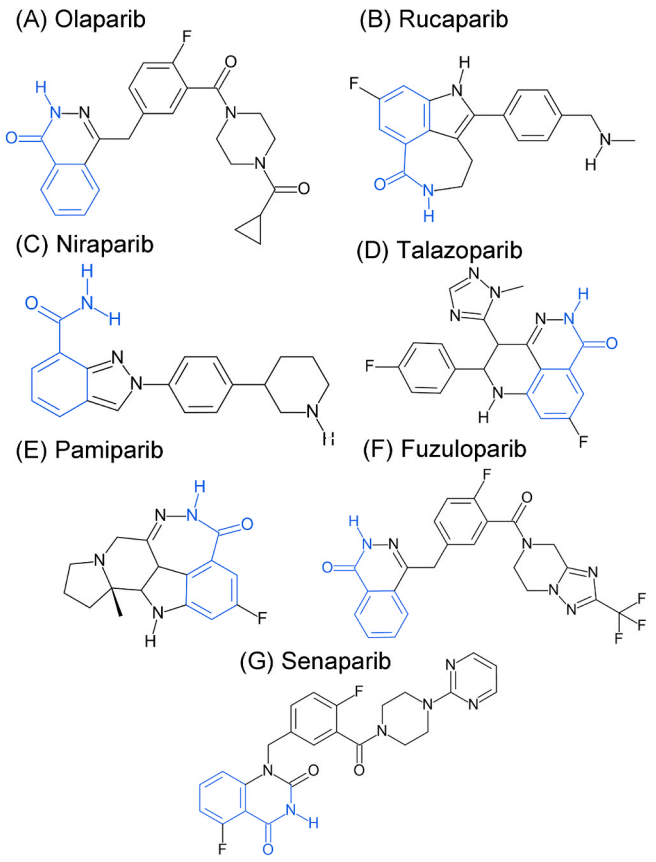

Fig. 6. Selected orally effective PARP1 inhibitors. (A–D) US FDA approved. (E–G) Chinese NMPA approved. The blue colored residues occupy the nicotinamide binding site of PARP1.

abdominal pain, decreased appetite, leukopenia, insomnia, headache, dyspnea, rash, hypertension, cough, dizziness, urinary tract infection, and hypomagnesemia [17]. Grade 3 or 4 adverse reactions included neutropenia (20 %), anemia (25 %), and thrombocytopenia (29 %). These side effects were managed by dose adjustments and supportive care.

3.2.4. *Talazoparib*

Talazoparib is a pyrido[4,3,2-*de*]phthalazin-3-one derivative (Fig. 5D) that is FDA approved for the treatment of breast and prostate cancer (Table 1). The drug has IC_{50} values of 0.57 nM and 0.58 nM for PARP1 and PARP2, respectively [31]. The X-ray crystal structure shows that the pyridazinone moiety of talazoparib mimics the amide group of nicotinamide in its interaction with PARP1. The drug forms hydrogen bonds with S904 and G863 (Fig. 6D). Tyr889 makes edge-to-face (π) interaction with the drug fluorophenyl group. E763, H862, G888, A898, K903, and E988 make van der Waals contact with PARP1. Moreover, V896, and Y907 interact hydrophobically with talazoparib. The daily dose of talazoparib is the lowest among the FDA approved PARP inhibitors at 0.5 mg; this reflects the high affinity of the drug for its target. It is also most effective among the approved drugs in trapping PARP1 to damaged DNA sites.

See Ref. [35] for a summary of the clinical trials that led to the FDA approval of talazoparib for the treatment of adults with suspected harmful or deleterious germline *BRCA*-mutated, HER2-negative, locally advanced or metastatic breast cancer as detected by an FDA-approved assay (BRACAnalysis CDx). This test facilitates the identification of patients with HER2-negative metastatic breast cancer who possess a germline *BRCA* mutation. Common adverse reactions (≥20 %) as a single agent including laboratory abnormalities include alopecia, fatigue, nausea, vomiting, diarrhea, headaches, decreased appetite, hemoglobin, neutrophils, lymphocytes, platelets and calcium, and increased blood glucose, aspartate aminotransferase, alkaline phosphatase, and alanine aminotransferase [17].

3.2.5. *Pamiparib*

Pamiparib is a complex heterocyclic system with a fluorene core fused with other rings, fluorine and several nitrogen atoms (Fig. 5E). The NMPA in China granted conditional approval of pamiparib for the management of ovarian, fallopian tube, or primary peritoneal cancers linked to germline *BRCA* mutations in 2021 for patients that had undergone at least two prior lines of chemotherapy (Table 2). Its IC_{50} values are 1.3 nM and 0.92 nM for PARP1 and PARP2 [31], respectively, indicating that it is a potent antagonist. The X-ray crystal structure shows that the drug hydrogen bonds with S904 and G863 (Fig. 6E). H862, F897, A898, K903 make van der Waals contact with pamiparib and E763, Y889, Y896, and E988 interact hydrophobically with the drug.

See Refs. [36,37] for a summary of the clinical trials that led to the Chinese NMPA approval of pamiparib (Partruvix™; BeiGene Ltd.) for the treatment of germline *BRCA* mutation-associated recurrent advanced ovarian, fallopian tube or primary peritoneal cancers previously treated with two or more lines of chemotherapy. Adverse reactions included anemia, neutropenia, leukopenia, thrombocytopenia, lymphopenia, nausea, vomiting, fatigue, diarrhea, and elevated aspartate aminotransferase and bilirubin levels. Hematological toxicities (cytopenias) occurred in ≥ 30 % of and patients were treated with dose adjustments and support measures.

3.2.6. *Fuzuloparib and senaparib*

Fuzuloparib is a pyrazine-phthalazine derivative (Fig. 5F) that was approved by the NMPA in China for the treatment of treatment of platinum-sensitive recurrent ovarian, fallopian tube, or primary peritoneal cancers in patients with germline *BRCA* mutation who have undergone second-line or greater chemotherapy (Table 2) [38]. The IC_{50} for PARP1 is 1.46 nM, indicating that it is a potent antagonist [38]. Common side effects include anemia, thrombocytopenia, neutropenia, leukopenia, lymphopenia, nausea, and fatigue.

Senaparib is a quinazoline derivative (Fig. 5G) that was approved by the NMPA in China for the maintenance treatment of advanced ovarian,

Table 2
Chinese NMPA approved orally bioavailable PARP blockers [a].

Generic (Brand Name) Company	NMPA approval year	Indications
Fuzuloparib (AiRuiY) Jiangsu Hengrui Pharmaceuticals Co., Ltd.	2020	Maintenance treatment of platinum-sensitive recurrent ovarian, fallopian tube, or primary peritoneal cancer in patients with g*BRCA* mutations who had undergone second-line or greater chemotherapy and (2021) treatment of recurrent platinum-sensitive ovarian cancer.
Pamiparib (Partruvix) BeiGene Ltd.	2021	Maintenance treatment of *gBRCA* mutation-associated ovarian, fallopian tube, or primary peritoneal cancer previously treated with two or more lines of chemotherapy.
Senaparib (Paishuning) Shanghai Junshi Biosciences Co., Ltd.	2025	Maintenance treatment of advanced epithelial high-grade ovarian, fallopian tube, or primary peritoneal cancer who achieved a complete or partial response after the completion of first-line platinum-based chemotherapy.

[a] *gBRCA,* germline breast cancer gene.

fallopian tube, or primary peritoneal cancers in patients who achieved a complete or partial response after the completion of first-line platinum-based chemotherapy (Table 2). The IC_{50} values for PARP1 and PARP2 are 0.48 nM and 1.6 nM, respectively [39]. The common side effects of senaparib are the same as those described above for fuzuloparib with the addition of constipation, diarrhea, and headaches. These are treated by dose adjustments and supportive therapy. X-ray crystal structures of these two PARP blockers are currently unavailable.

3.3. Cost of PARP inhibitors in the United States

The cost of PARP blockers is rather high. The average monthly cost for the four inhibitors is $15,500 with rucaparib being the lowest ($10,000) and talazoparib the highest ($19,500) (Table 3). The monthly cost of the PARP antagonists was obtained from www.pharmacychecker.com using the FDA label to determine the dosage and number of tablets required per day. The tabulated cost excludes any private or governmental insurance, which might cover the entire cost or more likely a fraction of the stated price. The cost of PARP blockers is somewhat lower than that of the protein kinase antagonists used to treat neoplastic disease with a monthly billing of $19,000 for neoplastic diseases and $7200 for nonneoplastic diseases, values from 2023 adjusted for medical inflation [40]. The above data show that the cost of targeted small molecule inhibitors is quite expensive and contributes to their financial toxicity. Financial toxicity refers to the financial hardship experienced by patients taking these drugs, which is especially so with cancer patients [41].

4. Physicochemical properties of orally bioavailable drugs

4.1. Lipinski's rule of five (Ro5)

Medicinal chemists and pharmacologists have investigated the physicochemical properties of medicinals that are orally bioavailable to learn how to formulate new orally efficacious medicines [42]. Lipinski's rule of five (Ro5) is an investigational methodology that is widely used to estimate membrane permeability and effectiveness in the drug-discovery setting [43]. It is a procedure that assesses drug-likeness and determines whether a compound with specific pharmacologic activities has characteristics suggesting that it would be orally effective. The Lipinski benchmarks were based on the knowledge demonstrating that most orally bioavailable drugs are comparatively small and moderately lipophilic in nature. The Ro5 is used during drug discovery as pharmacologically active lead candidates are optimized to improve their activity while maintaining target selectivity.

The Ro5 criteria suggest that less than ideal oral effectiveness is more likely to occur when (i) the AlogP (atom-based calculated Log P) is greater than 5, when (ii) there are more than 5 hydrogen-bond donors, when (iii) there are more than 5×2 or 10 hydrogen-bond acceptors, and when (iv) the molecular weight is greater than 5×100 or 500 [43]. The partition constant (P) is the ratio of the concentration of an un-ionized drug in the organic phase divided by its concentration in the aqueous phase of water-saturated *n*-octanol. The P value is related to the hydrophobicity of the drug, the greater the P value, the greater the hydrophobicity. The number of hydrogen-bond donors represents the total number of OH and NH groups. The number of hydrogen-bond acceptors is the number of nitrogen and oxygen atoms attached to at least one hydrogen atom in its neutral state. The Ro5 guidelines are based on

Table 3
Properties of commercial PARP inhibitors [a].

	Olaparib	Niraparib	Rucaparib	Talazoparib	Pamiparib	Fuzuloparib	Senaparib
Code name	AZD2281	AG-14447	MK4827	BMN-673	BGB290	SHR 3162	IMP4297
Tradename	Lynparza	Rubraca	Zejula	Talzenna	Partruvix	AiRuiY	Paishuning
Company	AstraZeneca	Clovis	GlaxoSmithKline	Pfizer	BeiGene Ltd.	Jiangsu Hengrui Pharm Co.	Shanghai Junshi Biosciences Co.
Year approved	2014 (FDA)	2016 (FDA)	2017 (FDA)	2018 (FDA)	2021 (NMPA)	2020 (NMPA)	2025 (NMPA)
PubChem CID	23725625	9931954	24958200	135565082	135565554	56649297	68389008
Formula	$C_{24}H_{23}FN_4O_3$	$C_{19}H_{18}FN_3O$	$C_{19}H_{20}N_4O$	$C_{19}H_{14}F_2N_6O$	$C_{16}H_{15}FN_4O$	$C_{22}H_{16}F_4N_6O_2$	$C_{24}H_{20}F_2N_6O_3$
MW	434	323	320	380	298	472	479
HD	1	2	2	2	2	1	1
HA	5	3	4	6	3	6	8
AlogP[b]	2.35	2.98	2.59	2.63	2.08	2.92	1.77
PSA (Å^2)	86.37	56.92	72.94	88.49	60.49	96.77	98.74
nStereo	0	0	1	1	1	0	0
Ki	5	1.4	3.8	0.57	1.3	1.46	0.48
p*Ki*	8.30	8.85	8.42	9.24	8.89	8.84	9.32
LipE	5.95	5.87	5.83	6.61	6.81	5.92	8.0
N	32	24	24	28	22	34	35
LE	0.366	0.520	0.495	0.465	0.460	0.367	0.323
Dose (mg/day)[c]	300 bid	600 bid	200 qd	0.5 qd	60 bid	150 bid	100 qd
Monthly cost in USA[d]	$14,000	$10,000	$18,500	$19,500	NA	NA	NA
Sol (μg/ml)[e]	60.1	11.4	14.9	101	93.3	16.5	62.6
nRotB	4	3	3	2	0	6	4
nRng	5	4	4	5	5	5	5
nAr	3	3	3	4	1	4	3
nBz	1	1	1	1	0	1	1
QED[f]	0.68	0.69	0.78	0.56	0.78	0.46	0.48
Complexity[g]	790	466	449	654	566	839	804

[a] FDA, US Food and Drug Administration HA, no. of hydrogen bond acceptors; HD, no. of hydrogen bond donors; LE, ligand efficiency; LipE, lipophilic efficiency; MW, molecular weight; N, no. of heavy atoms; nAr, no. of aromatic rings; NMPA, Chinese National Medical Products Administration; nRot, no. of rotatable bonds; nRng, no. of rings; nBz, no. of benzene moieties; nStero, no. of stereo centers; PSA, polar surface area from https://pubchem.ncbi.nlm.nih.gov/; Sol; solubility in water.
[b] From https://www.ebi.ac.uk/chembl/.
[c] From FDA label; bid, twice daily; qd, daily.
[d] From http:///www.pharmachecker.com; NA, not applicable.
[e] From https://go.drugbank.com/drugs/.
[f] QED, summed, weighted desirability (scores using MW + ALogP + HBD + HBA + PSA + nRotB + nAr) obtained from https://www.ebi.ac.uk/chembl/; see Ref. [51] for an extensive explanation.
[g] From https://pubchem.ncbi.nlm.nih.gov/.

the physicochemical properties of more than two thousand orally bioavailable drugs [43]. All commercial PARP antagonists obey the Ro5 criteria (Table 3).

4.2. The importance of lipophilicity and ligand efficiency

4.2.1. Lipophilic efficiency, LipE

After the publication of Lipinski's Ro5 in 2001 [43], subsequent studies of the chemical and physical properties of orally effective medicines have brought about numerous refinements [44–51]. For example, lipophilic efficiency, or LipE, is a property that is employed in drug development that combines potency and lipophilic-driven binding as a tactic to improve binding efficacy. The following equations define lipophilic efficiency:

$$\text{LipE} = \text{p}IC_{50} - \text{ALogP};\ \text{LipE} = \text{p}K_i - \text{ALogP}$$

Like the practice of describing the hydrogen ion concentration as pH, the p operator signifies the negative of the Log of the K_i or IC_{50}. The ALogP is the atom-based calculated Log of the Partition constant; this parameter quantifies the ratio of the drug content in the organic phase divided by its content in the aqueous phase of immiscible *n*-octanol/water.

The second term in the equation (– ALogP or minus ALogP) reflects the lipophilicity of a compound and the value is calculated using an algorithm based upon the characteristics of thousands of reference organic compounds. The greater the concentration of a drug in the organic phase when compared with the aqueous phase of a *n*-octanol/water mixture, the greater its lipophilicity is. Leeson and Springthorpe asserted that drug lipophilicity, as assessed by its – ALogP value, is an essential property that should be evaluated during drug discovery [45]. Large negative ALogP values are to be avoided because they reduce the lipophilic efficiency. Higher lipophilicity may lead to the binding of a drug to adventitious targets leading to increased toxicity. A common objective during drug development is to increase potency without simultaneously increasing lipophilicity [46].

The calculated ALogP of various drug candidates can be computed in seconds. Because experimental determinations of LogP are labor intensive, such measurements are not routinely performed. Hopkins et al. noted that satisfactory values for LogP are less than ~ 3 and reasonable values of lipophilic efficiency are greater than ~ 5 [46]. Increasing drug potency and decreasing lipophilicity usually produces products with improved pharmacological properties. The LogP values of the commercially available PARP antagonists are less than 3 and the LipE values are greater than 5.5 (Table 3).

4.2.2. Ligand efficiency, LE

The ligand efficiency (LE) relates potency, or binding affinity, to the number (N) of heavy (nonhydrogen) atoms in a drug [47]. The following formula is used to calculate this property:

$$\text{LE} = \Delta G^{\circ\prime}/\text{N} = -\text{RT ln } K_{eq}/\text{N} = -2.303\text{RT Log } K_{eq}/\text{N}$$

$\Delta G^{\circ\prime}$ is the standard free energy change of a drug binding to its target at neutral pH, R denotes the universal gas constant or energy-temperature coefficient (1.98×10^{-3} kcal/degree-mol), T is the temperature in degrees Kelvin, K_{eq} is the value of the equilibrium constant, and N represents the number of heavy atoms in the drug. The IC_{50} or K_i values are substitutes for the equilibrium constant. At a temperature of 37°C (310 K), this equation becomes $-(2.303 \times (1.98 \times 10^{-3}/\text{K}) \times 310\ \text{K Log } K_{eq})/\text{N}$ or $-1.41\ \text{Log } K_{eq}/\text{N}$. Ligand efficiency represents ligand potency based upon the average binding energy per heavy atom. The value of N is a proxy for the molecular weight. Ligand efficiency is useful in fragment-based drug discovery, and it aids in the design and selection of lead compounds for additional development [48].

Ligand efficiency is directly proportional to the binding affinity or – Log K_{eq} (a positive number) and is inversely proportional to the number of heavy atoms. Hopkins et al. reported that acceptable values for ligand efficiency (LE) are greater than 0.3 kcal per mole per heavy atom [44,46]. Ligand efficiency values for commercially available PARP blockers are all greater than 0.3 kcal per mole. The values for lipophilic efficiency (LipE) and ligand efficiency (LE) listed in Table 3 are based on results from different methodologies. Accordingly, these results cannot be used to make direct comparisons of the drugs owing to the different methodologies that were employed to obtain the data. These results were obtained, however, from various drug development studies and thus provide representative values.

4.2.3. Additional chemical descriptors of orally effective drugs

To establish drug properties related to oral effectiveness, the Ro5 prompted the development of many variations. For example, Veber et al. reported that the polar surface area (PSA) and the number of rotatable bonds differs between orally active and inactive compounds in a large series of drugs in rats [49]. They found that most orally effective medicinals have a polar surface area ≤ 140 Å^2 [49]. This property represents the sum of the surface over all polar atoms, primarily oxygen and nitrogen, and it also includes any bonded hydrogen atoms. The polar surface area of the commercially available PARP inhibitors is less than 100 Å^2 with a range of 56.92 (rucaparib) to senaparib 98.74 (Table 3). Moreover, they stated that an optimal number of rotatable bonds is 10 or fewer. This property modifies passive membrane permeation and reflects molecular flexibility or degrees of freedom. Furthermore, molecular flexibility is correlated with the entropy change that results from ligand binding and governs the quantity of drug bound to its targets. All approved PARP antagonists have fewer than 10 rotatable bonds (Table 3). The number of rotatable bonds ranges from 0 (pamiparib) to 6 (fuzuloparib). Furthermore, Oprea remarked that the number of ring structures (both aromatic and nonaromatic) in most approved orally bioavailable drugs is three or more [50]. All approved PARP blockers have four or more rings.

The molecular complexity of a compound is based upon its structure, its symmetry, and the elements it contains. The complexity is calculated using the Bertz/Hendrickson/Ihlenfelt algorithm [51–53]. Complexity is based upon the number of constituent atoms, the molecular structure, and the nature of the chemical bonds (single, double, triple, aromatic). Molecular complexity ranges from 0 for ions such as Zn^{+2} to several thousand for intricate natural products. Larger chemicals generally exhibit a greater molecular complexity than smaller compounds. The complexity values for the PARP blockers considered in this article were obtained from PubChem (https://pubchem.ncbi.nlm.nih.gov/). The molecular complexity of the PARP antagonists ranges from 466 (rucaparib) to 839 (fuzuloparib) (Table 3). There are no optimal or recommended molecular complexity values for orally bioavailable drugs; however, this property may be helpful in estimating the ease or difficulty of drug production, an important consideration in the manufacture of commercial pharmaceuticals.

Ritchie and Macdonald studied the role of aromaticity on the pharmacological properties of various medicinals within the viewpoint of drug design and discovery [54]. Aromaticity is related to cyclically conjugated organic compounds that are more stable than localized Kekulé structures owing to electron delocalization. These investigators considered aromatic bicyclic or tricyclic compounds as structures with two or three aromatic rings, respectively. Aromatic rings include substances containing carbon alone or with nitrogen or sulfur heteroatoms. These authors reported that increasing the number of carboaromatic rings had an unfavorable effect on pharmacologic properties by reducing aqueous solubility, increasing binding to serum albumin, and inhibiting cytochrome P450. The PARP inhibitors have 4 or 5 rings, from 1 to 4 aromatic rings, and 0 or 1 benzene moieties (Table 3).

Bayliss et al. evaluated the dose and water solubility for orally effective drug and drug candidates [55]. They reported that daily doses of 100 mg or less reduced the risk of toxicity. The dosages for PARP antagonists range from 1200 mg (rucaparib) to 0.5 mg (talazoparib)

(Table 3). Only talazoparib and senaparib meet the standard of 100 mg or less per day. Bayliss et al. reported that drugs with a water solubility of 100 μg/ml or less are associated with an increased risk of failure during drug discovery and clinical trials [55]. Only talazoparib, with a water solubility of 101 μg/ml fulfilled this criterion. The dosages among the approved PARP blockers spread over three orders of magnitude and the solubilities ranged over one order of magnitude.

5. PARP inhibitor resistance

PARP inhibitors are approved agents used in neoadjuvant, adjuvant, and maintenance therapies for the treatment of breast, ovarian, pancreatic, and prostate cancers [56]. They produce genetic interactions leading to synthetic lethality in BRCA-deficient cancers and in other cancers with defective DNA repair responses. PARP trapping onto DNA and PARP catalytic abrogation are the two main drivers of synthetic lethality associated with deficient BRCA activity. One advantage of synthetic lethality in BRCA-deficient tumors is the occurrence of cancer cell death while sparing normal cells. PARP blockers lead to the formation of a wide range of DNA lesions including double strand breaks, single-stranded DNA gaps, and stalled replication forks, eventually leading to cell death.

PARP inhibitors (PARPi) represent the first class of DNA damage response inhibitors to achieve clinical success in tumors with *BRCA1/2* mutations or homologous recombination deficiencies [57]. The development of drug resistance with disease progression within one-to-two years of therapy is a common challenge in most cancer patients with advanced disease. One resistance mechanism involves the restoration of homologous recombination, which is the most prevalent and significant mechanism of resistance. Reversion mutations in homologous recombination genes such as *BRCA1/2* can restore protein functionality by restoring homologous recombination repair capacity and reducing the therapeutic effects of PARP blockers. The data indicate that > 40 % of *BRCA*-mutated tumors that progress after PARP blockade bear *BRCA1/2* reversion mutations [58]. Using liquid biopsies or circulating cell-free DNA analysis, data show that these secondary mutations involve deletions or insertions that correct frame-shift mutations and restore the open reading frame of BRCA1/2 proteins thereby enabling full transcription and activity of these DNA repair proteins [59]. In metastatic castration-resistant prostate cancer patients bearing *BRCA* mutations that were treated with rucaparib, *BRCA* reversion mutations were detected in 39 % of them after progression, with higher rates associated with prolonged therapy, subclonal evolution, and clinical responses such as prostate-specific antigen-based improvements [60].

Resistance to PARP inhibitors can also arise through BRCA-independent mechanisms, including additional mutations in key homologous repair-related genes such as RAD51C, RAD51D, and PALB2, epigenetic modifications affecting repair pathways, or the functional loss of critical homologous repair suppressors, such MAD2L2 (also known as REV7) and p53-binding protein 1 (53BP1). These alternative routes evade BRCA dependency and add to the reactivation of homologous recombination, thereby undermining the therapeutic efficacy of PARP inhibitors [61].

Drug-resistant tumors may escape drug effects by altering PARP1 itself [57]. For example, PARP1 gene mutations or deletions can undermine drug binding and trapping to PARP1, rendering the drug ineffective. Various reports of PARP1 mutation-mediated resistance have been documented in clinical settings. Down regulation of PARP1 expression limits the overall amount of enzyme available to bind to damaged DNA. Studies suggest that resistant tumors may alleviate replication machinery blockade by increasing PARP1 degradation [57]. Furthermore, loss of PAR glycohydrolase activity mediates PARP antagonist resistance in homologous recombination-deficient malignancies by restoring PARP1 signaling [62]. Such losses have been described in triple-negative breast cancer and serous ovarian cancer.

As commonly observed in all forms of chemotherapy resistance, tumors can upregulate efflux pumps to reduce intracellular PARP antagonist concentrations [57]. For instance, BRCA1-deficient tumors frequently exhibit overexpression of ATP-binding cassette (ABC) transporters like ABCB1 (P-gp), ABCC1 (MRP1), and ABCG2 (BCRP). P-gp overexpression caused by *ABCB1* gene translocations/fusions has been observed in drug-resistant human breast and ovarian cancers, diminishing the efficacy of efflux-prone PARP antagonists such as olaparib and niraparib [63]. Furthermore, tumor cells may modify drug distribution or metabolism to decrease effective drug concentrations. See Refs. [57, 64] for comprehensive discussions of PARP inhibitor (i) clinical trials and (ii) drug resistance. As noted by Winer et al. “Biologically, the cancer cell is notoriously wily; each time we throw an obstacle in its path, it finds an alternate route that must then be blocked” [65].

6. Epilogue

PARP antagonists have become therapeutically important in cancer management, particularly for homologous recombination repair deficient neoplasms, such as *BRCA1/2*-mutated tumors [64]. We note, however, that PARP inhibitors have demonstrated progression free survival advantages in both newly diagnosed and recurrent cancers regardless of *BRCA1/2* mutation status though responses are more robust in *BRCA1/2*-mutated tumors [66]. Resistance to PARP inhibitors is the rule rather than the exception and current biomarkers such as *BRCA*-mutation status and homologous recombination scores – calculated from three parameters including (i) telomeric allelic imbalance (TAI), (ii) loss of heterozygosity (LOH), and (iii) large-scale state transitions (LST) – are insufficient in predicting long-term responses [57,66]. Despite reliance on *BRCA1/2* mutation status, about 50 % of *BRCA*--mutant tumors respond to PARP inhibitors. Meanwhile, most patients that are BRCA1/2-proficient are excluded from PARP inhibitor treatment. These data indicate that the determination of additional biomarkers would be helpful in predicting patient responses [67].

One approach to the management of various cancers involves the use of combination therapies. This strategy can lead to a more robust clinical response. On the other hand, it may lead to greater toxicities and adverse side effects. One therapy option involves the combination of monoclonal antibody immune checkpoint inhibitors (ICIs) with PARP antagonists. Durvalumab (Imfinzi), which is a human IgG1κ antibody that binds PDL1, has been used with olaparib in the study of patients with breast, colorectal, endometrial, and pancreatic cancers, cholangiocarcinomas, and leiomyosarcomas (clinicaltrials.gov). Pembrolizumab (Keytruda) is a humanized IgG4 monoclonal antibody that targets programed cell death protein 1 (PD-1), which binds to its ligands PDL1/ and PDL2. The monoclonal antibody is being evaluated in breast, cervical, colorectal, gastric, head and neck, pancreatic cancers, melanomas, and NSCLC in combination with olaparib. It is also being evaluated in the management of breast and ovarian cancers in combination with niraparib. Nivolumab (Opdivo) is a human IgG4κ monoclonal antibody that targets PD-1 and is being evaluated with (i) rucaparib for the treatment of ovarian, fallopian tube, and peritoneal, endometrial, and prostate cancers and with (ii) niraparib for pancreatic adenocarcinomas. Atezolizumab (Tecentriq) is a humanized IgG1κ monoclonal antibody that targets PDL1 and is in clinical trials in combination with niraparib for the management of small cell lung and ovarian carcinoma and with olaparib for the treatment of breast cancer (clinicaltrials.gov). Although these drugs are FDA approved, the combination regimens are not currently approved.

Drugs other than PARP inhibitors are under evaluation for the treatment of DNA damage, alone or in combination with other agents [68]. Several ATM antagonists including AZD1390, M4076, WSD-0628, AZD0156, and XRD-0394 are in clinical trials for various neoplasms. The latter compound is a dual ATM and DNA-PK inhibitor. Camonsertib is an ATR blocker that is being evaluated in combination with niraparib or olaparib for homologous recombination (HR) biomarker selected tumors. Ceralasertib is another ATR blocker that is being evaluated in the management of NSCLC, melanoma, and ovarian cancers in combination

with olaparib and durvalumab. Several CHK7 inhibitors including LY3143921, TAK-931, LBS-007, TQB3824, and LY2880070 are under clinical evaluation for various malignancies. AZD7648 and peposertib are DNA-PK blockers in clinical trials targeting solid tumors and advanced malignancies. Several WEE1 inhibitors including IMP7068, SY-4835, adavosertib, azenosertib, and debio0123 are in clinical trials targeting solid tumors. See Ref. [68] for a full description of the clinical trials associated with these non-FDA approved orally efficacious medicinals.

PARP inhibitors are well-established in the management of selected malignancies, but they are associated with hematologic toxicities, the development of primary and secondary resistance, and approval for only four tumor types [68]. Development of selective PARP1 inhibitors – lacking PARP2/3 action – promises to lead to better patient outcomes with diminished toxicities and more durable therapeutic benefits. Other DNA damage repair agents that exploit synthetic lethality show considerable promise. ATR and WEE1 antagonists are among the most advanced therapeutics in clinical trials, which may lead to approvals by regulatory agencies. Combining DNA damage response inhibitors with other therapeutic modalities including immunotherapies and small molecule protein kinase blockers represents a promising new strategy. As clinical trials and experimentation uncover novel drug combinations along with the development of better biomarkers, new synthetic lethal strategies have the potential for broadening treatment options and improving outcomes in patients with various cancers.

CRediT authorship contribution statement

Robert Roskoski: Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization.

Declaration of Competing Interest

Charles B. Huggins was an instructor of mine at the University of Chicago. The author is unaware of any affiliations, memberships, or financial holdings that might be perceived as affecting the objectivity of this review.

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Data availability

No data was used for the research described in the article.

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