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The “Pushmi-Pullyu” of DNA REPAIR: Clinical Synthetic Lethality

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Abstract

Maintenance of genomic integrity is critical for adaptive survival in the face of endogenous and exogenous environmental stress. The loss of stability and fidelity in the genome caused by cancer and cancer treatment provides therapeutic opportunities to leverage the critical balance between DNA injury and repair. Blocking repair, and pushing damaged DNA through the cell cycle using therapeutic inhibitors, exemplifies the “pushmi-pullyu” effect of disrupted DNA repair. DNA repair inhibitors can be separated into five bio-functional categories: sensors, mediators, transducers, effectors, and collaborators that recognize DNA damage, propagate injury DNA messages, regulate cell cycle checkpoints, and alter the microenvironment. The result is cancer therapeutics that takes advantage of clinical synthetic lethality, resulting in selective tumor cell kill. This manuscript reviews recent considerations related to DNA repair and new DNA repair inhibition agents and organizes those findings to address future directions and clinical opportunities.

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Keywords

DNA damage repair; homologous recombination defects; DNA damage response; genomic instability; mutational burden; synthetic lethality

Opinion

The “pushmi-pullyu” of DNA repair

What allows individuals to be so remarkably different, yet so very similar, is their genomic variability. Such variability, encoding brown versus blue eyes, blond versus brown hair, and other traits, occurs from normal selection for genomic variants. The hallmark of our longevity and responsiveness to environmental and other exposures is our genomic stability, plasticity and genomic vigilance. This stability is the result of ongoing monitoring, recognition, and response to genomic changes, through a series of DNA recognition and repair pathways [3]. Repair is a normal and necessary function in numerous cellular compartments. The ability of our immune cells to respond to and remember antigen stimulation is associated with purposeful real time genomic remodeling. However, such ongoing normal events also have the potential to inadvertently introduce genomic variability and opportunity for genomic injury. It is estimated that cells may have more than 20,000 single strand DNA break (SSB) events per day, with a small fraction going on to double strand breaks (DSB) [4, 5].

Mammalian cells have evolved a number of DNA damage repair pathways with independent, selective and specific purposes, while also interweaving key proteins and interactions [6, 7]. DNA repair pathways are on the lookout for injury and have the responsibility to repair DNA damage or declare futility and trigger apoptosis. This dynamic between DNA damage and repair creates tension within the cell, much like the mythical pushmi-pullyu of Dr. Doolittle [8]:

“Yes,” said the pushmi-pullyu—“to the Abyssinian Gazelles and the Asiatic Chamois—on my mother’s side. My father’s great-grandfather was the last of the Unicorns.”

But you could not do this with the pushmi-pullyu—because, no matter which way you came towards him, he was always facing you.

DNA injury is one head of the pushmi-pullyu, the head opposing DNA damage repair. Genomic stability is the fulcrum between injury and repair.

TP53 has been called “the guardian of the genome” as it is one of the first proteins to be activated with early SSB events [9–11]. Under normal circumstances, its phosphorylation and activation leads to a halt in the cell cycle to allow DNA repair to occur. This *stop and wait* sign is lost when *TP53* is mutated, an early and frequent occurrence in a large proportion of solid tumors. In such cases, the genomic injury is not repaired and is carried into progeny cells. Accumulation of DNA damage is also a trigger for necroptotic death and mitotic catastrophe, depending upon the type of damage [12, 13].

DNA damage and repair pathways

DNA damage and repair pathways have evolved from the less complex prokaryote and lower eukaryote process to a series of distinct and interactive pathways [14]. These DNA repair pathways are the toggles between cell cycle arrest for either repair or apoptosis, and propagation of damage via its conversion into permanent injury. Pathways have specialized to recognize specific subsets of single strand DNA error and repair, such as mismatch repair, limited base errors, and crosslinks [3, 15] (Figure 1). Independent pathways for double strand repair, homologous recombination repair (HR), a high fidelity repair used when there is a sister chromatid available, and the pathways of non-homologous end-joining, which are repair pathways of convenience, where the DNA is just re-linked [15], also exist.

Protein and enzymatic modulators of DNA repair pathways have five roles (Text Box 1 and Table 1) [15, 16]. **Sensor proteins** recognize and flag injury, to initiate the DNA damage repair and recruit proteins to activate the repair response. **Mediators** are multifunctional and exert their effects in more than one phase of cell cycle progression. **Signal transducers** are enzymes that control the activity of the cell cycle checkpoints and DNA repair pathways; transducers relay and amplify these damage signals along adjacent chromatin structures. **Effectors** permit and/or repair DNA injury and block progression through the cell cycle, and may lead to accumulation of mutations and damage result in genomic instability [5, 17, 18]. The **collaborators** may be important in modulating the immune and oxygen-regulated angiogenesis of the cellular microenvironment. They harness the microenvironment, angiogenesis and alter the immune environment. The processing of genomic and genetic injury is a therapeutic opportunity. It has been well leveraged over the decades with the development of classical chemotherapies that cause injury to DNA via crosslinking, intercalation, nucleotide-mimetic substitution, or prevention of nucleotide production [19]. Chemotherapy works to drive injury to irreparable levels, preferentially in cancer cells. Now, the category of **DNA repair inhibitors, DNARi**, is demonstrating clinical activity, especially in the categories of sensors, mediators, transducers, and effectors.

Text Box 1

What defines clinical synthetic lethality and DNA repair inhibitors

- Clinical synthetic lethality: common underlying event that causes a gain- or loss-of-function phenotype or drug that, when combined with a drug targeted to a mutation or dysfunctional pathways augments antitumor effects
- The “pushmi-pullyu” effect of DNA repair
 - DNA damage repair pathways collaborate to oversee DNA fidelity and activate damage repair
 - DNA damage accumulates due to injury and inhibition of repair; this triggers apoptosis or mitotic catastrophe
 - The push and pull between damage and repair inhibition creates a window of opportunity for therapeutic intervention
- Bio-functional classification of DNA repair inhibitors (DNARi's)

- Sensor-drugs block recognition of DNA injury
- Mediator-drugs block damage recognition and repair
- Transducer-drugs block injury message propagation in the cell cycle
- Effector-drugs permit and/or repair DNA injury and block cell cycle progression
- Collaborator-drugs or microenvironment events cause a loss- or gain- of-function phenotype altering expression of DNA damage repair proteins or cell cycle regulators

Figure I. Bio-functional Classification of DNA Repair Inhibitors
The drugs used to block DNA repair can be categorized by their functions in maintaining genomic fidelity. *Sensors* recognize DNA damage and create flags to signal injury presence. They secondarily participate in recruitment of proteins to *mediate* activation of the DNA repair pathways. *Mediators* are multifunctional and exert their effects in more than one phase of the cell cycle progression mediated by the cell cycle checkpoints. Signal *transducers* are enzymes, such as polymerases, kinases, and phosphatases, that control the activity of the cell cycle checkpoints after DNA damage and/or effect physical change on the DNA, such as exonuclease or ligase functions. *Effectors* block the progression through the cell cycle under normal conditions, to allow for DNA repair. Dysregulation of such effectors with rapid movement through the cell cycle may lead to accumulation and propagation of deleterious mutations and subsequent damage resulting in genomic instability. The *collaborators* may be important in modulating the immune

and oxygen-regulated cellular microenvironment such as to either augment injury, activate immune response to neoantigens, or provide reactive oxygen species. Abbreviations: PARP1/2, poly(ADP-ribose) polymerase 1/2; RAD1/9/17, RAD1 checkpoint DNA exonuclease, RAD9 checkpoint clamp component, RAD17 checkpoint clamp loader component; BRCA1, BRCA1, DNA repair associated; TP53BP1, tumor protein p53 binding protein 1; MRN complex, MRE11-RAD50-NBS1 complex; ATM, ATM serine/threonine kinase inhibitor; ATR, ATR serine/threonine kinase inhibitor; RAD51, RAD51 recombinase; H2AX, H2A histone family member X; CHEK1/2, checkpoint kinase 1/2; WEE1, WEE1 G2 checkpoint kinase

DNA repair inhibition as a therapeutic target

DNA repair is one side of the DNA stability see-saw. The possibility of targeting key elements of DNA repair pathways for therapeutic benefit gained traction after the recognition that disruption of the poly(ADP) ribose polymerase (PARP) sensor signal could selectively injure cells deficient in HR due to mutational loss of *BRCA1* and *BRCA2* function [20, 21]. This class of agents built on the biology of competitive inhibition of NAD, necessary for function of the PARP enzyme, went from preclinical concept to first international approval for patient use in approximately one decade. It also was the first-in-class of the DNARi class of cancer therapeutics.

Normal cellular homeostasis revolves around the recognition of injury, the first key checkpoint of sensors. TP53 is a central checkpoint protein, responsible for stopping cell cycle activity to allow for activation of repair pathways, functioning as a mediator, transducer, and indirect effector (Figure 2). *TP53* is also the most frequently mutated gene in solid tumors, with both gain-of-function and loss-of-function mutations promoting dysfunctional cell cycle progression and pushing conversion of mutational injury into permanent genome injury [16, 22]. Attempts at recovering p53 function, initially by gene therapy introduction of wild type transcripts were unsuccessful [23], and now alternative methods to regulate the DNA repair recognition checkpoints are being developed.

The new therapeutic direction of DNARi can be defined functionally by the five categories in Text Box 1 and Table 1. The first class of anticancer drugs targets the sensors, agents that interrupt injury recognition. Agents in this category include inhibitors of pathways that flag DNA injury, exemplified by olaparib, the PARP inhibitor. The second class of drugs block mediators of DNA damage repair and includes, for example, inhibitors of ATM and ATR. These proteins translate the message of PARylation to coordinate generation of a further message. DNARi that block message transducers, the third class, prevent or limit signals that recruit repair proteins, can include inhibitors of CHEK1 and CHEK2, and WEE1, affecting the cell cycle indirectly and linking cell cycle regulation with DNA repair. The fourth group of inhibitors block the effector proteins, such as cell cycle checkpoint regulators, the cyclin dependent kinases, and CHEK1/2 and WEE1, to block the normal cell cycle stop signals allowing cells to focus energy into DNA repair. The direct inhibition of WEE1 kinase and CHEK1/2 kinases and their interaction with DNA injuring agents, and with other DNARi,

augments injury and pushes cells through the cell cycle, locking in DNA injury [5, 16]. The final category contains the collaborators, those modulators that promote DNA damage production indirectly. Key examples in this class are the drugs inhibiting angiogenesis and those that modulate immune activation through immune checkpoint inhibitors. Hypoxia promotes DNA injury through multiple potential mechanisms ranging from transcriptional downregulation of DNA repair proteins such as BRCA1 and BRCA2, production of reactive oxygen intermediates, and genomic instability and mutator phenotypes [24, 25]. The latter events may promote neoantigen production, recognized by the awakened immune system in the case of immune checkpoint inhibitor therapy.

Clinical synthetic lethality

Clinical synthetic lethality pushes the concept of synthetic lethality from pairs of *Drosophila* mutations to treatment paradigms for the cancer clinic. Drugs that cause a loss- or gain-of-function phenotype coupled with cancer specific genomic events, or drugs that are genotypically injurious can result in tumor cell kill. The context of the therapeutic opportunity is important in optimizing selective anti-tumor effects. Examples of six opportunities are described wherein a cellular-endogenous event or an environmental-exogenous event occurs that either initiates or propagates DNA injury. That injury may synergize with DNARi to create clinical synthetic lethality (Text Box 2/Figures 3 and 4).

Text Box 2

Clinical synthetic lethality and therapy in oncology

Investigators most often factor in synergy and antagonism, or additivity and super-additivity, rather than synthetic lethality, when developing combination therapies in cancer cell lines or animal models. Synthetic lethality was originally described when two or more separate mutations in *Drosophila* models led to organism death; whereas, as a single mutation was compatible with viability [1]. The concept of synthetic lethality was further described by McLornan et al. to include chemical interactions and contextual changes [2]. We now advance this to clinical synthetic lethality, which focuses on generating anticancer treatments with a wide therapeutic index, sparing normal cells while killing tumor cells. Clinical synthetic lethality either screens for or uses drugs that cause a change of function phenotype, which collaborates clinically with drugs or tumor environments that are injurious. DNA is altered either endogenously by propagation of germline events or somatic mutation, or exogenously through exposures and modifiers that cause DNA and chromosomal damage. Interruption of normal genomic vigilance and repair prevents normal correction of those abnormalities. This can occur through blocking signals of DNA injury, transduction of the signal to the repair complex, or prevention of proper function of the repair complex. Progression through the cell cycle without arrest for repair is one example of prevention of repair complex function; such progression maintains the DNA injury and can promote subsequent mitotic catastrophe and cell death. Complexing DNA injury with dysfunctional or absent DNA repair creates the opportunity for augmenting DNA damage to a lethal level in the tumor cell

preferentially. Thus, clinical synthetic lethality translates the ideas of chemical and contextual synthetic lethality into novel therapeutic regimens for cancer patients.

Preexisting or endogenous cellular loss- or gain-of-function events (Figure 4) can be leveraged by the introduction of DNARi to maximize injury, drive cell death, and promote neoantigen production while sparing normal cells. Examples of this include accumulated tumor or germline genomic errors; such is seen with deleterious germline mutations in *BRCA1* or *BRCA2*. Tumors arising in this background sustain a second injury and have a loss of function essential to normal HR function. Resultant cancers are more susceptible to DNA injury, such as platinum chemotherapy exposure [26], or inhibition of DNA repair, such as PARPi treatment [27]. Similar data are emerging with somatic mutations in the SWI/SNF complex gene *ARID1a* [28], with a potential for loss or reduced HR function and potential increased contextual clinical synthetic lethality [29]. Another opportunity for a cooperative interaction with DNARi is somatic amplification or mutation in cell cycle proteins causing dysfunctional cell cycle dynamics and replication stress. This has been demonstrated with amplification of cyclins D and E in breast and ovarian cancers [30–32]. The presence of pluripotent oncogenic drivers, such as mutation in *TP53* or *Rb*, may also result in altered cell cycle dynamics that may confer potential for augmentation of injury in a DNARi background, such as the use of a WEE1 inhibitor [33, 34]. Lastly, patients whose tumors have a high mutational load or burden may be more susceptible to immune checkpoint inhibitors with DNARis, and combinations of these agents are now in clinical trials [5].

Exogenous events also can synergize with DNARi for clinical benefit within the tumor milieu (Figure 4). Radiation and/or chemotherapy create DNA damage; that damage by itself may be insufficient to induce cell death. Preclinical and clinical data indicate that inclusion of DNARi agents, such as PARPi or inhibitors of the G2/M checkpoint kinases, WEE1 or CHEK1, can be additive and/or synergistic with radiation and chemotherapy to improve outcome [33, 35, 36]. The addition of WEE1 kinase inhibition to radiation increases cell injury, with further injury when cisplatin is added [33, 37, 38]. Interestingly, some of the DNARi, such as WEE1 kinase inhibitors, have had limited activity as single agent treatments. Some increase in activity was observed in patients with *BRCA1/2* mutations, and/or in combination with DNA damaging agents such as platinum, demonstrating both endogenous and exogenous clinical synthetic lethality with DNARi [39, 40]. Such combinations may, however, result in increased normal cell toxicity and studies optimizing the scheduling of these combinations may be needed to yield optimal patient benefit.

A major exogenous opportunity for therapeutic interaction is altering either the tumor stromal or immune microenvironments. A clinically robust example is found with the collaboration between DNARi and angiogenesis inhibition. Inhibition of VEGF receptors 1, 2, and 3 by the VEGFR tyrosine kinase inhibitor cediranib alters local hypoxia; cediranib markedly improved clinical outcome in ovarian cancer patients when combined with the PARPi, olaparib [41]. The mechanisms behind this successful combination are still being elucidated, and induction of endothelial cell precursors indicate that hypoxic injury was occurring [42]. Hypoxia downregulates the expression of *BRCA1*, which may in part

explain this drug combination's interaction [24]. There also is anticipated synergistic interaction between DNARi-injured cells and the local tumor immune microenvironment [43, 44]. DNARi propagate any existing DNA injury within the tumor by the dysregulation of DNA repair and/or altered cell cycle kinetics preventing the time for repair necessary or optimal repair (Figure 3).

Stabilizing such mutations creates the opportunity for the presentation of clonal and subclonal neoantigens to tumor infiltrating immune cells [45, 46]. Combining a selective antigen-rich environment with immune checkpoint inhibitors to overcome tumor immune tolerance is a novel clinical synthetic lethality approach currently in early phase clinical development. Here, the DNARi augment a locally rich immune milieu and the immune checkpoint inhibitor revises the local immune microenvironment to reactivate immune surveillance, to recruit CD8⁺ T cells, and to reduce Treg suppressor cells. This may be further enhanced by the pharmacological manipulation of transcription, driving increased expression of these neoantigens. The presence of such immunogenic neoantigens increases in tumors with a high mutational load, and immune (re)activation may be more likely to occur (Figure 3). Leveraging DNA damage repair inhibition while pushing cancer cells toward cell cycle arrest, apoptosis and mitotic catastrophe leads to the perfect storm in the tumor microenvironment and synthetic lethality in clinical settings.

Selection paradigms to optimize clinical synthetic lethality

Selection of patients for treatment with DNARi's using markers of homologous repair defects have started. At present, only deleterious germline *BRCA1/2* mutations are considered predictive, prognostic, and fit-for-purpose when selecting patients for treatment with PARPi. Controversy still surrounds the definition of tumor *BRCA1/2* mutation as the requirement for homozygosity has not been clarified. This selective/enrichment biomarker has been validated in clinical trials in patients with breast and ovarian cancer [47, 48]. A variety of commercial laboratory assays are available for identifying deleterious BRCA mutations. NGS or whole exome/genome sequencing panels to be used to identify mutations in DNA repair genes are easily in reach, though have not been comprehensively or prospectively validated in large prospective clinical trials to confirm their predictive or prognostic significance, except in men with prostate cancer where germline screening is being recommended [49, 50].

The development of selection and enrichment biomarkers for HRD and other mutations is a high priority in clinical trials with combinations of drugs selected to target synthetic lethality. Approaches using bioinformatics analyses of tumor genomics may identify synthetic lethal interactions. Exceptional responders should be evaluated using exome/transcriptome and whole genome including functional studies to determine the unique nature of response [51]. For example, response to platinum therapy is associated with nucleotide excision repair defects in ovarian cancer [52]. The development of targeted screening tools, prevention treatment strategies for germline carriers and identification of agents that create loss of function phenotypes that selectively decrease DNA repair in tumor with limited or no impact in normal cells are just three examples of strategies to implicate clinical synthetic lethality.

A hybrid homologous recombination deficiency (HRD) score was built using weighted values from measures of loss of heterozygosity (LOH), telomeric imbalance (TAI), and large-scale state transitions (LST) [41, 53–55]; validation of this HRD score is anticipated soon. Evaluation of this HRD score was included as a prospectively planned objective of the NOVA study of niraparib, a PARPi, for treatment of high grade ovarian cancer patients. Recent developmental applications of this HRD score have suggested it may be applicable to triple negative breast cancer [55], and endometrial cancers.

Concluding Remarks

Clinical synthetic lethality can be broadly defined as an underlying event often seen in cancer that causes a gain- or loss-of-function phenotype or drug that, when combined with a drug targeted to a mutation or dysfunctional pathways augments antitumor effects. The dynamic interplay between DNA damage and repair inhibition, “pushmi-pullyu”, creates a window of opportunity for therapeutic intervention resulting in more than incremental improvement in clinical outcome (see Outstanding Questions box). Categorizing DNA repair inhibitors bio-functionally based on the role they play in DNA repair as sensors, mediators, transducers, effectors and collaborators, allows clinical cancer researchers to directly evaluate the inhibitors role in DNA repair and its associated interactions with other DNARi’s and the tumor microenvironment. Leveraging clinical synthetic lethality hopefully will lead to improved patient outcomes and survival.

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Figure 1. Hypoxia-Regulated DNA Repair

During DNA replication, translation and transcription, as well as during epigenetic and post-translational modification, DNA is repaired using a number of pathways including HR, MMR, NER, BER, NHEJ, and TLS. DNA repair protein expression is sensitive to and modulated by hypoxia and oxia. In hypoxic conditions, DNA repair pathway protein expression is decreased in many instances, and NER, BER and NHEJ proteins involved in the DNA damage response are increased. The primary point of action for specific agents and inhibitors are indicated by repair pathways, damage response, and as a function of the stage of DNA replication and modification. During replication and repair, the hypoxic microenvironment may predispose to a loss of function phenotype.

Abbreviations: HR, homologous recombination; MMR, mismatch repair; NER, nucleotide excision repair; BER, base excision repair; NHEJ, non-homologous end joining; TLS, translesion synthesis; RAD51, RAD51 recombinase; BRCA2, BRCA2, DNA repair associated; RAD51B/C, RAD51 paralogs B and C; XRCC3, X-ray repair cross complementing 3; RAD52, RAD52 homolog DNA repair protein; MLH1, mutL homolog 1; PMS1, postmeiotic segregation increased 1; MSH6, mutS homolog 6; RAD23B, RAD23 homolog B; APE1, apurinic/apyrimidinic endonuclease 1; OGG1, 8-oxoguanine DNA glycosylase; MYH, mutY DNA glycosylase; NEIL2, nei like DNA glycosylase 2; NUDT1, nudix hydrolase 1; XRCC6, X-ray repair cross complementing 6; XRCC5, XRCC5, X-ray repair cross complementing 5; DNA-PKcs, DNA-dependent protein kinase catalytic subunit; FANCD2, fanconi anemia complementation group D2; NBN, nibrin; ERCC1, excision

repair cross-complementation group 1; XPA, xeroderma pigmentosum, complementation group A; XPC, xeroderma pigmentosum, complementation group C; POLI, DNA polymerase iota; i, inhibitor; ATRi, ataxia telangiectasia and Rad3-related kinase inhibitor ; ATMi, ataxia telangiectasia mutated kinase inhibitor ATM serine/threonine kinase inhibitor; DNA-PKi, DNA-dependent protein kinase inhibitor; POLE, DNA polymerase epsilon; ARID1a, AT-rich interaction domain 1A; EZH2i, enhancer of zeste homolog 2 inhibitor; PARPi, poly(ADP-ribose) polymerase inhibitor; CHEK1/2i, checkpoint kinase 1/2 inhibitor; chemo, chemotherapy; RT, radiotherapy; HDACi, histone deacetylase inhibitor

Abbreviations: i, inhibitor; DNARi, DNA repair inhibition; CHEK1, checkpoint kinase 1 inhibitor; CHEK1/2i, checkpoint kinases 1/2; WEE1, WEE1 G2 checkpoint kinase; MYT1, myelin transcription factor 1; CDK1/2, cyclin dependent kinases 1/2; CDK4/6/9, cyclin dependent kinases 4/6/9; ATR, ataxia telangiectasia and Rad3-related kinase; DNA-PKCS, DNA-dependent protein kinase catalytic subunit; MDM2, MDM2 proto-oncogene; TP53, tumor protein p53.

Figure 3. Targets of Opportunity in DNA Damage Response (DDR) and Homologous Recombination Deficiency (HRD)

Endogenous and Exogenous DNA abnormalities and injury result in the DNA damage response and DNA repair, and lead to cell cycle arrest. Arrest of the cell cycle may result in apoptosis or mitotic catastrophe. These events provide targets of opportunity for the treatment of genomically unstable cancer through the inhibition of DNA repair (DNAR) and cell cycle (CC) progression. DNA repair inhibitors (DNARi) block enzymes and proteins critical for DNA replication and repair including PARPi, CDK4i, Wee1i, CHEK1/2i, ATMi, ATRi and DNA-PKcsi.

Abbreviations: DNAR, DNA repair; i, inhibitor; DNARi, DNA repair inhibitor; PARP, poly(ADP-ribose) polymerase; PARPi, poly(ADP-ribose) polymerase inhibitor; ATR, ATR serine/threonine kinase; ATM, ATM serine/threonine kinase; DNA-PKcs, DNA-dependent protein kinase catalytic subunit; CCi, cell cycle; CHEK, checkpoint kinase; CHEK1/2i, checkpoint kinase 1/2 inhibitor; ATMi, ATM serine/threonine kinase inhibitor; ATRi, ATR serine/threonine kinase inhibitor; DNA-PKcsi, DNA-dependent protein kinase catalytic subunit inhibitor; WEE1, WEE1 G2 checkpoint kinase; WEE1i, WEE1 G2 checkpoint kinase inhibitor; CDK4/6, cyclin dependent kinase 4/6; CDK4/6i, cyclin dependent kinase 4/6 inhibitor; SWI/SNF, switching defective/sucrose nonfermenting; ARID1a, AT-rich interaction domain 1A; SMARC, SWI/SNF related, matrix associated, actin dependent regulator of chromatin; MYC-BETi, MYC and bromodomain and extra-terminal inhibitor; DDR, DNA Damage Response; p53^{mut}, tumor protein 53 mutated; CCND, cyclin D; CCNE, cyclin E

Figure 4. Endogenous and Exogenous Modulators of Clinical Synthetic Lethality

A circos plot cartoon is used to describe the relationship between endogenous and exogenous inducers or modulators of DNA damage. This DNA damage may collaborate with DNA repair inhibition to create a clinical synthetic lethal event. Endogenous effectors include genomic instability, somatic/germline mutations, cell cycle defects and oncogenic drivers; whereas, exogenous effectors include the events within the cancer cell microenvironment, immune- or tumor/vascular/stromal-mediated DNA injury, and exogenous processes such as ambient or therapeutic radiation and chemotherapeutics. Abbreviations: TOP1/2i, topoisomerase 1/2 inhibitor; i, inhibitor

Table 1

Classes of DNA repair inhibitors, DNARi

	Pathways	Targets	Agents/Inhibitors
SENSORS	DNA damage recognition		
		PARP	olaparib, niraparib, rucaparib, veliparib talazoparib
MEDIATORS	DNA injury message propagation		
		ATM	AZD0156
		ATR	VX-970, AZD6738
		DNA-PK _{cs}	CC-115, MSC2490484A
TRANSDUCERS	DNA injury message propagation		
		ATM	
		ATR	
		DNA-PK _{cs}	
	Cell cycle checkpoint regulation		
	G1/S	CHEK1	SCH-900776/MD8776
		CHEK2	LY2606368
		CDK4/6/9	palbociclib, dinociclib, abemaciclib
	G2/M	CHEK1/2	LY2606368, PD-0332991, prexasertib
		WEE1	AZD1775
		CDK1/2	AG-024322, AT7519, flavopirodol, Eisai7070, SCH
EFFECTORS	Cell cycle checkpoint regulation		
	G1/S	CHEK1	
		CHEK2	
	G2/M	CHEK1/2	
		WEE1	
	p53	Mdm2	
		Antagonists	Nutlin-3, Nutlin-3a, YH239-EE, NVP-CGM097, RG7112, SAR299155, RG7388, AMG232, DS-3032b, MK8242
		Activators	NSC207895
COLLABORATORS	Altered microenvironment (e.g., angiogenesis and immune)		
		VEGF ligand blockers	bevacizumab
		VEGFR inhibitors	cediranib, sunitinib, pazopanib, others
		Immune checkpoint inhibitors	pembrolizumab, nivolumab, durvalumab, atezolimumab, ipilimumab, tremelimumab