Molecular Pathways: Targeting PARP in Cancer Treatment

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Abstract

Poly (ADP-ribose) polymerases (PARPs) are a family of nuclear protein enzymes involved in the DNA damage response. The role of PARP-1 in base excisional repair has been extensively characterized. More recent in vitro studies additionally implicate a role for PARP-1 in facilitating homologous recombination and non-homologous end-joining. The more faithful process of homologous recombination repair of double-stranded DNA breaks, involves localization of BRCA-1 and BRCA-2 to sites of DNA damage, resection of the double-stranded break, and gap-filling DNA synthesis using the homologous sister chromatid as a template. Simultaneous dysfunction of both DNA repair pathways decreases the ability of cells to compensate, and forms the basis for the concept of synthetic lethality. Treatment strategies thus far have focused on two main principals: 1) exploitation of the concept of synthetic lethality in homologous recombination deficient tumors, primarily in breast and ovarian cancer patients with BRCA mutation, and 2) as radio-sensitizers and chemo-sensitizers. BRCA deficiency accounts for only a fraction of dysfunction in homologous recombination repair. Epigenetic alterations of BRCA function and defects within the Fanconi anemia pathway also result in defective DNA repair. Rational therapeutic combinations exploiting alternate mechanisms of defective DNA repair, abrogation of cell cycle checkpoints, and additional functions of PARP-1, present novel opportunities for further clinical development of PARP inhibitors. Based on the results of clinical studies of PARP inhibitors thus far, it is imperative that future development of PARP inhibitors take a more refined approach, identifying the unique subset of patients that would most benefit from these agents, determining the optimal time for use, and identifying the optimal combination partner in any particular setting.

I. Background

The integrity of the human genome is constantly under stress from both endogenous genotoxic insults such as reactive oxygen species generated during normal metabolism, or from exogenous insults such as chemotherapeutic agents. Cellular response depends upon the magnitude of the insult, resulting in induction of cell cycle checkpoint pathways and DNA repair mechanisms. If the damage is extensive and irreparable, induction of cell death occurs. Poly (ADP-ribose) polymerases (PARPs) are a family of nuclear protein enzymes involved in the post-translational modification of proteins and synthesis of poly (ADP-ribose). PARP-1 and PARP-2 are the best characterized members of the PARP family, and play a key role in the DNA damage response and repair of single-stranded breaks (SSBs) through base excisional repair (BER).

The role of PARP-1 in BER has been the most extensively. After binding to SSBs, PARP-1 transfers the ADP-ribosyl moiety from NAD+ to acceptor proteins, generating long chains of poly (ADP-ribosyl)ated polymers. This allows for the recruitment of DNA repair proteins such as DNA polymerase β, DNA ligase III, and scaffolding proteins such as x-ray cross complementing protein 1 (XRCC1) to sites of SSBs (1,2). PARP may also facilitate homologous...
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recombination (HR) via recruitment of factors like ataxia telangiectasia-mutated (ATM), mitotic recombination 11 (Mre11), and Nijmegen breakage syndrome 1 (Nbs1) to sites of double-stranded DNA damage (3), and has been shown to interact with the DNA protein kinase complex involved with non-homologous end-joining (NHEJ) (4) [Figure 1]. More recent studies by Helleday et al. propose that PARP inhibition results in trapping of PARP-1 on DNA repair intermediates at SSBs and stalling of replication forks that require BRCA-dependent HR for resolution (5). The more faithful process of HR repair, involves localization of BRCA-1 and BRCA-2 to sites of DNA damage, resection of double-stranded breaks (DSBs), and gap-filling DNA synthesis using the homologous sister chromatid as a template. Whereas, in NHEJ, DNA break ends are directly ligated without the use of a homologous template, resulting in the introduction of errors at ligated sites. DSBs, which can occur during repair of SSBs or secondarily from chemotherapeutic agents or ionizing radiation, are the most critical form of DNA damage and can result in problems for transcription and replication, eventually leading to apoptosis (6).

Loss of PARP activity in and of itself is not lethal to cells with intact HR pathway, as unrepaired SSBs are converted to DSBs which can be effectively repaired via the HR pathway. The concept that a double-hit in DNA repair would result in synthetic lethality is the rationale for investigating PARP inhibition in BRCA 1/2 mutated cell lines deficient in HR. BRCA-1 plays a role in the surveillance of DNA damage and transduction of DNA repair responses whereas BRCA-2 plays a direct role in DNA repair, via modulation of Rad51, which is involved in double-stranded repair by HR (7). Cells that are deficient in BRCA-1 or BRCA-2 are rendered defective in the ability to repair through HR and depend upon error-prone NHEJ for DNA repair. The resultant amplification of DNA instability and chromosomal aberrations results in cell death. This concept of synthetic lethality was first reported in two landmark studies in 2005 (8, 9). Investigators showed that inhibition of PARP-1 both by chemical inhibition and siRNA depletion in embryonic stem cells lacking BRCA 1 or BRCA 2 resulted in generation of chromatid breaks, G2 cell cycle arrest, and enhancement of apoptosis.

II. Clinical-Translational Advances

PARP inhibitors currently in clinical development compete with the nicotinamide moiety of NAD+ for the catalytic domain of the PARP enzyme. This prevents its release from sites of DNA damage and therefore, prevents DNA repair enzymes from accessing the site. Olaparib (AZD-2281/KU-0059436) and veliparib (ABT-888) have been the most extensively studied in clinical trials. Additional PARP inhibitors currently under active clinical investigation also include niraparib (MK-4827), CEP-9722, E7016/GPI-21016, BMN-673, and rucaparib (AG-014699/PF-01367338). Iniparib (BSI-201) was initially studied in triple negative breast cancer (TNBC) (10); however, recent evidence suggests iniparib does not inhibit PARP-1 and PARP-2 at clinically relevant doses, and is no longer considered a PARP inhibitor (11). Given the variable potency of current PARP inhibitors in clinical development, it is not known to what degree of PARP inhibition is needed for maximal efficacy, and to what degree the off-target effects beyond PARP inhibition contribute to antitumor effect. A sandwich immunoassay to measure levels of poly(ADP-ribose) macromolecules (PAR) in both peripheral blood mononuclear cells (PBMCs) and tumor has been developed to determine on target effect of the
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PARP inhibitors (12, 13). γH2AX levels and caspase 3 levels are also currently being evaluated as surrogate markers of efficacy.

Treatment strategies thus far have focused on two main principals: 1) exploitation of the concept of synthetic lethality in HR deficient tumors, primarily in BRCA mutation-related breast and ovarian cancers, and 2) as radio- and chemotherapy-sensitizers. Early Phase I studies evaluating single-agent olaparib in a cohort of patients enriched for BRCA 1/2 mutation carriers demonstrated clinical benefit in 12 of 17 (63%) with objective responses in 9 of 19 (47%) patients (14). In the expansion cohort of 50 BRCA mutation carriers with ovarian, peritoneal, and fallopian tube cancer, 46% received clinical benefit, with the highest benefit rate noted in patients with platinum-sensitive disease (15). Pharmacodynamic assays demonstrated more than 90% reduction of PAR levels in PBMCs at a dose of 60mg administered on a twice daily dosing schedule implicating on target effect.

The concept of PARP inhibition in sporadic cancers with epigenetic loss of BRCA function has also been evaluated (16, 17). In a phase 2 study evaluating olaparib in ovarian and TNBC patients stratified for the presence or absence of BRCA-1 or BRCA-2 mutation, of the 63 evaluable patients, objective responses were seen in 11 of 46 (24%) patients with no BRCA mutation, all in high-grade serous ovarian cancer, supporting the notion that alternative mechanisms for failure of HR may also predispose sensitivity to PARP inhibition (18). Similar findings have also been demonstrated with veliparib and niraparib. In the Phase I study evaluating continuous dosing of veliparib in patients with BRCA 1/2 mutated cancer, platinum-refractory ovarian cancer, and basal-like breast cancer, 1 partial response (PR) and 7 stable diseases (SD) were seen in 25 patients with no BRCA mutation (19). In the Phase I study evaluating niraparib in advanced solid tumors enriched for sporadic cancers associated with non-BRCA HR repair defects, there were 3 PR and 4 SD of the 20 evaluable patients (20).

The majority of clinical development of PARP inhibitors thus far, has focused on PARP inhibitors as chemo-sensitizers in combination with alkylating agents, topoisomerase inhibitors, platinum agents, and/or anthracyclines (21-31; Table 1). The use of rucaparib, olaparib and veliparib in combination with chemotherapy has been burdened with increased myelosuppression. This raises the question of whether the addition of PARP inhibitor improves efficacy in the presence of decreased doses of chemotherapy. The randomized study of temozolomide and veliparib did not show improvement in overall survival over temozolomide alone (32). Another issue concerns the correlation between PAR levels and activity. A multicenter randomized trial comparing metronomic cyclophosphamide with or without veliparib showed no improvement in response rates of the combination, despite demonstration of 50% reduction of PAR levels in 9 of 10 patient PBMCs (33). One reason could be the lack of tight correlation between the PAR levels in PBMCs and tumor. Less myelosuppressive chemotherapy combinations and off target effects of PARP inhibitors are currently being investigated.

Extensive preclinical data also exists for PARP inhibition and augmentation of cellular radio-sensitivity (34-39). Radio-sensitization of a non-Hodgkin’s lymphoma cell line has been shown with olaparib or veliparib in combination with both external beam radiation and 131I-tositumomab (35). Radio-sensitization with veliparib has been demonstrated in head and neck
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carcinoma cell lines (36) and lung cancer xenograft models (37), with niraparib in neuroblastoma cell lines (38), and with E7016 in combination with temozolomide and radiotherapy in a glioma mouse model (39). A clinical trial is ongoing evaluating veliparib in combination with whole brain radiation therapy in patients with brain metastases. Of 48 evaluable patients, best tumor response was seen in 37.5% in non-small cell lung carcinoma and 52.9% in breast cancer patients (40). No enhanced toxicity was noted unlike the myelosuppression seen with chemotherapy making this approach more attractive for further investigation.

III. Future Directions

The majority of clinical development of PARP inhibitors thus far, has been limited to the setting of relapsed disease. More recently, olaparib has been studied in the maintenance setting. In a phase 2 study, patients with platinum-sensitive relapsed, high-grade serous ovarian cancer were randomized to receive either maintenance olaparib at 400mg twice daily dose or placebo. Progression-free survival was longer with olaparib (median of 8.4 months) versus placebo (median 4.8 months) [HR of 0.35, CI 0.25-0.49, P< 0.001] (41). Given the tolerability of single agent treatment and with evidence indicating activity with treating bulk and small volume disease in high-risk patients with known BRCA 1/2 mutation, the question of PARP inhibitor as a preventative agent has been raised. A major obstacle in evaluating PARP inhibitors in prevention is the concerns for risk of secondary malignancy. This will be answered as more data becomes available on the long term use of PARP inhibitors.

In addition, BRCA deficiency accounts for only a fraction of causes of defective HR repair. Additional causes include defects in other HR pathway proteins, alterations of proteins involved in the Fanconi anemia (FA) pathway, defects of proteins in the sensing of DNA damage, as well as in the cell cycle checkpoints (42). Early in vitro studies of phosphatase and tensin homolog (PTEN) null cells implicated a role for Rad51-mediated double-stranded DNA repair, and sensitization to PARP inhibition similar to BRCA-deficient cells (43). PTEN mutations are common in multiple cancers in addition to endometrial cancers and glioblastomas (44). The mechanism by which PTEN loss results in genomic instability may involve perturbations of multiple DNA repair pathways, presenting a unique opportunity for further development of PARP inhibitors in this subset of patients. A study of abiraterone and veliparib in metastatic castration-resistant prostate cancer is currently underway to further explore this concept (ClinicalTrials.gov identifier: NCT01576172).

The complex interaction between various components of the Fanconi pathway and other pathways involved in HR presents an opportunity to expand upon the subset of patients that may benefit from PARP inhibition. In response to DNA damage, a nuclear complex of FA proteins form, culminating in the downstream ubiquination of FANCD2 that is required for repair of DNA crosslinks and interaction with BRCA2 and DNA repair (45). Inactivation of the FA pathway through methylation of the FANCF promoter (46-48) has been detected in a number of sporadic cancers. Additional epigenetic alterations affecting FANCC expression in 53% of early-onset and 59% of late-onset sporadic breast cancers have also been identified (49). Studies are ongoing to evaluate this concept by testing patients with somatic deficiency in FA pathway with veliparib with or without mitomycin C (50).
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Evidence also exists for sensitivity to PARP inhibition in the setting of defective detection of DNA damage and abrogation of cell cycle checkpoints. Cyclin-dependent kinase 1 (Cdk1), a key component of cell cycle regulation, phosphorylates BRCA1 forming BRCA1 foci at sites of DNA damage to facilitate checkpoint activation. Recent preclinical studies show inhibition of Cdk1 activity sensitizes BRCA-proficient cancers to PARP inhibition (51). The addition of Cdk1 inhibition to olaparib resulted in synergistic inhibition of growth of TNBC cells in vitro (52). A phase I trial of veliparib and SCH727965 is ongoing to evaluate this concept (ClinicalTrials.gov identifier: NCT01434316). Additional in vitro evidence also exists for sensitivity to PARP inhibition in the setting of deficiency of ATM involved in the initial detection of DNA damage, as well as checkpoint kinase 2 (Chk2), the downstream effector of cell cycle arrest (42). With the initial promise of PARP inhibitor in BRCA deficient patients, other populations are being investigated as well as combinations with other targeted agents.

More recent evidence suggests pleiotropism of PARP inhibition, and additional off-target effects of PARP inhibitors. In addition to playing a central role in DNA repair, preclinical evidence additionally implicates a role for PARP in angiogenesis. In vitro studies showed inhibition of PARP resulted in enhancement of VEGF protein expression on endothelial cells (53) and inhibition of growth-factor stimulated migration and proliferation of human umbilical vein endothelial cells (54). PARP inhibition also resulted in down-regulation of genes involved in angiogenesis during skin carcinogenesis in mice (55). A phase I study combining olaparib with cediranib, a multi-targeted kinase inhibitor of VEGFR-1/2/3 and c-kit, in recurrent ovarian and TNBC, showed a 56% unconfirmed response rate in the cohort of ovarian cancer patients, but with hematologic dose-limiting toxicities (56). Recent comparative analyses of rucaparib, olaparib, and veliparib in TNBC cell lines suggest target pleiotropism of the various PARP inhibitors, and implicate additional PARP-independent signaling mechanisms thought to account for differing levels of anti-tumor activity (57). In this study, rucaparib demonstrated the highest antitumor potency in all cell lines evaluated, and was distinct in its ability to suppress Stat3 phosphorylation at concentrations of 2.5uM. Additional evidence suggests rucaparib and veliparib may also target the NF-κB pathway (58, 59). In response to DNA damage, NF-κB is activated via signaling cascades, culminating in the transcriptional modulation of genes involved in cellular proliferation. Aberrant NF-κB activation is thought to contribute to chemoresistance in multiple cancers (60). Recent cell viability assays evaluating veliparib in HR proficient HER2+ breast cancer cell lines demonstrate cytotoxicity with evidence of inhibition of NF-κB at the transcriptional level at concentrations of 10uM (59). Further investigation into PARP-independent off-target effects of PARP inhibition is ongoing.

IV. Conclusions

Clinical development of PARP inhibitors in combination with chemotherapy thus far have been limited by the fact that when used in combination with chemotherapeutic agents, they could not be used in full doses due to enhanced myelosuppression, often requiring dose reduction of the partnered cytotoxic agent. The question of whether PARP inhibitor combinations in the setting of dose reduction is superior to full dose therapy without PARP inhibitor needs to be addressed in future studies. In addition, given the variable potency of current PARP inhibitors in
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clinical development, the degree of PARP inhibition needed for maximal efficacy, and to what degree the off-target effects are contributing to antitumor effect is not known. Based on known data to date, it is imperative that future development of PARP inhibitors take a more refined approach, identifying the unique subset of patients that would most benefit from these agents: determining the optimal time for use, identifying the optimal combination partner in any particular setting, and the optimal population. Further investigation is needed with regard to how various additional DNA repair pathways interact and whether synthetic lethality may be utilized in this setting as well. Further delineation of off-target effects of current PARP inhibitors may present additional opportunities for drug development. Finally, identification and screening for mechanisms of resistance, reactivation of HR by secondary mechanisms, and alternate DNA repair pathways which may compensate for loss of PARP activity would allow for optimal use of the PARP inhibitors in an oncologic setting.
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Figure 1. After binding to SSBs, PARP-1 transfers the ADP-ribosyl moiety from NAD+ to acceptor proteins, generating long chains of poly (ADP-ribosyl)ated polymers. This allows for the recruitment of DNA repair proteins such as DNA polymerase β, DNA ligase III, and scaffolding proteins XRCC1 to sites of SSBs. PARP may also facilitate homologous recombination via recruitment of factors like ATM, Mre11, and Nbs1 to sites of double-stranded DNA damage, and has been shown to interact with the DNA protein kinase complex involved with non-homologous end-joining. ATM, ataxia telangiectasia-mutated; BER, base excision repair; DNA-PKcs, DNA-protein kinase catalytic subunit; DSB, double-strand break; HR, homologous recombination; Mre11, mitotic recombination 11; Nbs1, Nijmegen breakage syndrome 1; NHEJ, non-homologous end-joining; PPi, inorganic pyrophosphate; SSB, single-strand break; XRCC1, x-ray cross complementing protein 1. (Adapted by permission from Macmillan Publishers Ltd: Nature Reviews Cancer (61), copyright 2010.)
Table 1 – Key Clinical trials of PARP Inhibitors in Combination with Various Chemotherapeutic Agents and Related Hematologic Toxicities.

CR = complete response, MR = moderate response, PR = partial response, SD = stable disease,

<table>
<thead>
<tr>
<th>Combination</th>
<th>Tumor Type</th>
<th>Response</th>
<th>Hematologic Toxicity</th>
<th>Trial Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I: ABT-888 (Veliparib) + Topotecan</td>
<td>Advanced solid tumors and lymphomas</td>
<td>CR: none reported PR: none reported SD: 4/24</td>
<td>DLT: neutropenia thrombocytopenia; 3 of 6 pts enrolled on DL1 experienced DLTs Gr 3/4: neutropenia 20.8% febrile neutropenia 8.3% thrombocytopenia 12.5%</td>
<td>Starting dose of: Veliparib 10mg PO BID D1-7+ Topotecan 1.2mg/m2/day D1-5</td>
</tr>
<tr>
<td>Phase I: ABT-888 (Veliparib) + Irinotecan</td>
<td>Advanced solid tumors</td>
<td>CR: none reported MR: 2/28 PR: 5/28 SD: 10/28</td>
<td>DLT – febrile neutropenia leucopenia neutropenia</td>
<td>Escalating doses of Veliparib PO BID D1-14 + irinotecan 100mg/m2 D1,8</td>
</tr>
<tr>
<td>Phase I: ABT-888 (Veliparib) + doxorubicin + cyclophosphamide</td>
<td>Breast cancer and advanced solid tumors</td>
<td>CR: none reported PR: 3/18 (TNBC; BRCA mutation) SD: 8/18 (breast cancer)</td>
<td>DLT – febrile neutropenia</td>
<td>Escalating doses of Veliparib 50-150mg PO BID D1-4 + doxorubicin 60mg/m2 D3 + cyclophosphamide 600mg/m2 D3</td>
</tr>
<tr>
<td>Phase I: ABT-888 (Veliparib) + Oral Cyclophosphamide</td>
<td>Advanced solid tumors and lymphomas</td>
<td>CR: none reported PR: 7/35 (6 BRCA mutation) SD: 6/35 (3 BRCA mutation)</td>
<td>Gr 2-4 lymphopenia 34.3%</td>
<td>Escalating doses of Veliparib 20-80mg PO daily for 7,14,or 21 days + escalating doses of cyclophosphamide 50-100mg for 21 days</td>
</tr>
<tr>
<td>Phase II: ABT-888 (Veliparib) + Temozolomide (TMZ)</td>
<td>Metastatic breast cancer</td>
<td>(unconfirmed) CR: 1/24 PR: 2/24 SD: 7/24</td>
<td>Gr 3/4: neutropenia 11.4% thrombocytopenia 20%</td>
<td>Veliparib 40mg PO BID D1-7 TMZ 150mg/m2 PO daily D1-5</td>
</tr>
<tr>
<td>Randomized, double-blind, placebo-controlled trial ABT-888 (Veliparib) + Temozolomide (TMZ) vs.</td>
<td>Metastatic melanoma</td>
<td>No statistically significant improvement in PFS or OS</td>
<td>Gr 3/4 hematologic toxicities: TMZ alone 38% Veliparib 20mg + TMZ 54% Veliparib 40mg + TMZ 57%</td>
<td>1:1 randomization to: Placebo BID + TMZ, or Veliparib 20mg BID + TMZ, or Veliparib 40mg BID + TMZ</td>
</tr>
</tbody>
</table>
| Phase I: | TMZ alone | Middleton M et al. (2011) | Stage I: advanced solid tumors | CR: 1/32  
PR: 2/32  
SD: 7/32 | No DLTs  
Mycelosuppresion seen in 13% pts with rucaparib 18mg/m²/day + TMZ 200mg/m²/day | Stage I: TMZ 100mg/m²/day + escalating doses rucaparib to PARP inhibitory dose (PID)  
Stage I: Rucaparib fixed at PID + TMZ escalating doses up to 200mg/m²/day |
| Phase I: | AG-014699/PF-01367338 (Rucaparib) + Temozolomide (TMZ) | Plummer R et al. (2008) | Stage II: chemo-naïve metastatic melanoma |  |  |  |
PR: 2/21 (1 BRCA mutation)  
SD: none reported | DLT: febrile neutropenia,  
thrombocytopenia;  
2 of first 3 pts enrolled on DL1 experienced DLTs  
Gr 3/4: neutropenia 61%  
lymphopenia 61%  
thrombocytopenia 57% | Starting dose of:  
Olaparib 100mg PO BID D1-4  
Gemcitabine 500mg/m² D3-10  
Cisplatin 60mg/m² D3 |
| Phase I: | AZD-2281 (Olaparib) + Carboplatin | Lee J et al. (2011) | BRCA-1/2 mutation carriers breast and ovarian cancer | CR: none reported  
PR: 8/23 (ovarian cancer)  
3/4 (breast cancer)  
SD: 11/23 (ovarian cancer)  
1/1 (breast cancer) | DLT: thrombocytopenia and delayed neutropenic recovery  
Gr 3/4: Anemia 10%  
Thrombocytopenia 20%  
Neutropenia 17% | Escalating doses of olaparib continuously or D1-7 + escalating doses of carboplatin (AUC 3-5) on D2 or D8 |
| Phase I: | AZD-2281 (Olaparib) + Dacarbazine | Khan OA et al. (2011) | Advanced solid tumors; Expansion phase in chemo-naïve stage III/IV melanoma | CR: 0/40  
PR: 2/40  
SD: 8/40 | DLT: neutropenia,  
thrombocytopenia  
Gr 3/4: Anemia 5%  
Neutropenia 22.5%  
Thrombocytopenia 7.5% | Escalating doses of Olaparib 10-100mg PO BID D1-7 + Dacarbazine 600-800mg/m² D1 |
| Phase I/II: | AZD-2281 (Olaparib) + Paclitaxel | Dent RA et al. (2010) | Triple negative breast cancer | CR: none reported  
PR: 7/19  
SD: none reported | DLT: neutropenia requiring dose delay and GCSF prophylaxis | Olaparib 200mg PO BID +  
Paclitaxel 90mg/m² IV weekly for 3 of 4 weeks; |
PARP1 DNA strand break detection by PARP1
Binding of PARP1 to DNA strand breaks
PARP1 PARP inhibitors
Nicotinamide
Poly(ADP-ribosyl)ation of PARP1

Transient recruitment and noncovalent and covalent modifications of various proteins

XRCC1, Histone H1, DNA-PKcs, Ku70 and Ku80, ATM, MRE11, Topoisomerase I

Recruitment of XRCC1 and DNA ligase III to SSBs and repair by BER
Altered chromatin binding during DNA damage and transcription
DSB repair by NHEJ
DSB repair by HR and checkpoint activation
HR and restarting of collapsed replication forks
Genomic maintenance
Other unknown targets

CCR Molecular Pathways