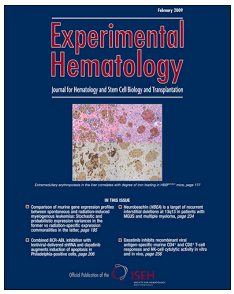
Accepted Manuscript



PARPi-induced synthetic lethality for acute myeloid leukaemia treatment

Lu Zhao, Chi Wai Eric So

PII: S0301-472X(16)30509-4

DOI: 10.1016/j.exphem.2016.07.007

Reference: EXPHEM 3439

To appear in: *Experimental Hematology*

Received Date: 27 May 2016

Revised Date: 13 July 2016

Accepted Date: 17 July 2016

Please cite this article as: Zhao L, Eric So CW, PARPi-induced synthetic lethality for acute myeloid leukaemia treatment, *Experimental Hematology* (2016), doi: 10.1016/j.exphem.2016.07.007.

PARPi-induced synthetic lethality for acute myeloid leukaemia treatment

Lu Zhao[a] and Chi Wai Eric So[a]

[a] Leukaemia and Stem Cell Biology Group. Department of Haematological Medicine, King's College London, Denmark Hill campus SE5 9NU, London UK

Correspondence:

Chi Wai Eric So, Ph.D. Professor and Chair in Leukaemia Biology
Department of Haematological Medicine,
King's College London/King's College Hospital
Denmark Hill, London SE5 9NU, U.K.
Telephone number: (44) 020 78485888
email: eric.so@kcl.ac.uk

Category for the Table of Contents: Malignant Hematopoiesis

Word Counts: 2026

PARPi-induced synthetic lethality for acute myeloid leukaemia treatment

Lu Zhao and Chi Wai Eric So

Leukaemia and Stem Cell Biology Group. Department of Haematological Medicine, King's College London, Denmark Hill campus SE5 9NU, London UK

Corresponding author: eric.so@kcl.ac.uk

Abstract

Genomic instability is one of the most common and critical characteristics of cancer cells. The combined effect of replication stress and DNA damage repair defects associated with various oncogenic events drives genomic instability and the disease progression. However, these DNA repair defects found in cancer cells can also provide unique therapeutic opportunities, which also form the basis of synthetic lethal targeting of solid tumours carrying BRCA mutations. While the idea of utilising synthetic lethality as a therapy strategy has been gaining momentum and progress in various solid tumours, its application in leukaemia still largely lags behind. In this article, we will review the recent advances in understanding the roles of DNA damage response in acute myeloid leukaemia (AML) and examine the potential therapeutic avenues of using PARP inhibitors in AML treatment.

Keywords: AML, PARPi, synthetic lethality, BRCA, MLL leukemia, AML1-ETO, APL, PML-RARA, GSK3 inhibitors, HOXA9, MEIS1, MLL

Introduction

Poly (ADP-ribose) polymerase (PARP) 1 and PARP2 belongs to the PARP protein superfamily that catalyses the polymerisation of ADP-ribose onto their target substrates using oxidized nicotinamide adenine dinucleotide (NAD^+) as a co-substrate and releasing nicotinamide as a by-product. This posttranslational modification often regulates the conformation, stability and/or activity of the targeted proteins (*1*). Therefore, PARP1 is involved in a wide array of cellular processes ranging from DNA repair, gene transcription regulation to cell division. However, the best well characterised role of PARP1 is in single stranded break (SSB) repair in the DNA damage response (DDR) pathway (*2*). PARP1 initiates this process by detecting and binding to the SSBs. Catalytic activity of PARP1 and PARP2 results in the PARsylation of PARP itself and a series of additional proteins involved in DDR. The rationale of using PARP inhibitors (PARPi) for cancer treatment has previously been suggested by studies from Ashworth's and Helleday's groups (*3, 4*). This relies on their abilities to selectively kill BRCA1 or BRCA2 mutated breast or ovarian cancers with a defective repair of double stranded breaks (DSBs) by homologous recombination (HR) (*5*). Upon PARP inhibition, SSBs are continuously generated by endogenous oxidants, replication and oncogenic stresses, and can no longer be efficiently repaired by the base excision repair (BER) in which PARP1 and PARP2 play a key role. SSBs become DSBs as DNA polymerases travel along the replication forks. Normal cells are able to repair the DSBs by HR and survive. In contrast, HR-deficient BRCA1 or BRCA2 mutated cancer cells accumulate excessive DNA damages that are either unattended or repaired by the error-prone non-homologous end-joining (NHEJ) pathways leading to genomic instability and eventual cell death (*1*) (Figure 1). In addition, it has also been reported that certain PARPi can trap PARP proteins onto DNA breaks which induces replication fork collapses (*6*). Thus, the concomitant inhibition of PARP activity in cancer cells with defective HR can induce synthetic lethal conditions providing a potential therapeutic strategy for a wide range of cancers including leukaemia.

Targeting cancer genomes by PARPi-induced synthetic lethality

With many PARPi currently being developed and tested in clinical trials, Lynparza (olaparib) is the only FDA approved drug for treatment of *BRCA1* or *BRAC2* mutated ovarian cancer, and is at the most advanced stage of targeted therapy for triple negative breast cancer

patients. In addition to BRCA mutated cancers, the therapeutic potential of using PARPi also extends to cancers bearing mutations affecting other key components of HR including ATM, ATR, CHK1, RAD51 along with their homologues and the FANC family proteins. PARPi was reported to have activity in cells defective in several of these proteins (*7*). While mutations affecting classical HR genes can only been found in small subtypes of cancers (*8*), the continuous exploration of novel player in DNA damage responses reveals an unexpectedly critical function mediated by PTEN, one of the most commonly mutated tumour suppressors in human cancer. While cytoplasmic PTEN antagonizes PI3K signalling pathway for tumour suppression, nuclear PTEN regulated by SUMOylation and ATM phosphorylation mediates DNA repair upon exposure to IR or DNA damaging agents (*9*). Cells lacking nuclear PTEN were hypersensitive to DNA damage, and were susceptible to killing by a combination of genotoxic stress and PI3K inhibitors. While these findings may extend the potential application of synthetic lethality in a wider range of cancer subtypes, PTEN and HR gene mutations can only be found in a very small fraction of AMLs (*9*), which is frequently driven by mutated transcription factors and epigenetic regulators (*10*). Given the critical functions of transcriptional deregulation in acute leukaemogenesis, we and others have speculated the potential application of synthetic lethality approach to target the compromised DDR, resulted from aberrant transcriptional networks, in the leukaemic cells (*8*).

Targeting aberrant transcriptional programmes in leukaemia by PARPi-induced synthetic lethality

There is compelling evidence that chimeric transcription factors found in AML result in repression of one or several DDR pathways leading to genomic instability. AML1-ETO, which accounts for about 10% of adult AML, is found to repress a variety of genes involved in DDR in particular proteins involved in BER (*OGG1, FEN1, MPG, POLD2*) and HR pathway (*ATM, RAD51, BRCA1*) (*11, 12*) . These defects in DDR are accompanied with high level of DNA damage characterised by the γH2AX and an increase in mutation frequencies (*11-15*). Similarly, PML-RARα fusion in acute promyelocytic leukaemia (APL) represses a large array of genes in DDR such as in the BER pathway (*FEN1, LIG3, MPG OGG1*), and HR (*RPA1, BRCA1, RAD51*) (*11, 16*) . Studies from Zhong et al. also suggest that PML is essential in multiple steps of HR (*17*). Loss of PML impairs the recruitment of MRE11, RPA1, BRCA1, and RAD51 to DNA damage foci, whereas PML-RARα directly disrupts the

localisation and activity of BLM and PML. RAD51 protein levels were also downregulated upon PML knockdown in another study, indicating that PML might be required for RAD51 stability (*18*). Strikingly, PML counteracts HAUSP function in regulating PTEN ubiquitinylation and nuclear localization via the adaptor protein DAXX that inhibits HAUSP-mediated deubiquitinylation of PTEN (*19*). While PML promotes nuclear location of PTEN, expression of PML-RARα fusion can suppress PML function and PTEN nuclear localization.

Using mouse primary transformed cells and human leukaemic cells, we along with others further demonstrated specific suppression of HR transcriptional programmes and accumulation of excessive DNA damage in AML1-ETO or PML-RARα leukaemic cells, which were uniquely sensitive to PARPi treatment both *in vitro* and *in vivo* (*14*). Consistently, Kasumi-1 cells expressing AML1-ETO were less sensitive to PARPi upon AML1-ETO knockdown (*20*). Moreover, PARPi as a mono-therapy exhibited strong oncogenic suppression property of ATRA-resistant APL cells both *in vitro* and *in vivo* in a xenograft model, extending the potential application of PARPi for treatment resistant APL (*14*). On the other hand, abberant suppression of other DDR mediators in leukaemia cells may also be permissive for PARPi-induced leathality. While PTEN mutations are not common in AML, reduced expression of PTEN has been implicated in BCR-ABL induced chronic myeloid leukiemia (CML) (*21*) and PTEN-deficient mice developed myeloproliferative disorders and acute leukaemias (*22, 23*). PTEN was found to be important for the expression of RAD51 (*24*). It was shown that PTEN-defficient cells are extremely sensitive to PARPi providing the rationale for ongoing studies of using PARPi in PTEN defficient tumours (*25, 26*). On the other hand, Faroani et al. reported undetectable BRAC1 and BRAC2 protein expression and reduced expression mRNA expression in primary AML patient samples, suggesting BRCAness phenotype due to transcriptional and/or translational repression of BRCA1 and BRCA2 (*27*). Moreover, a reduced BRCA1 expression due to promoter hypermethylation was also reported in therapy-related AML cells that might be sensitive to PARPi (*28*). Therefore, these findings provide a strong rationale to apply PARPi for leukaemia treatment.

Combination therapy with PARPi for refractory AML

In addition to utilising PARPi as a monotherapy in specific AML subtype, there are potential scopes of combining PARPi with other inhibitors for AML. As compared to

AML1-ETO or PML-RARα leukaemic cells, leukaemia driven by MLL fusion proteins that activate expression of HR genes in part via *HOXA9* are resistant to PARPi treatment (*14*). We showed that modulation of HOXA9 transcription activity could synergize with PARPi in targeting MLL rearranged leukaemia. Suppression of *Hoxa9* by genetic approach or inhibiting one of its co-regulators, glycogen synthase kinase 3 (GSK3) could sensitise MLL rearranged leukaemic cells to PARPi treatment. Combination of GSK3 inhibitor, Li_2CO_3, and PARPi could robustly suppress MLL-AF9 leukaemia and significantly extended the disease latency in both primary syngeneic mouse model and primary human MLL leukaemia xenotransplant model. Therefore simultaneously targeting of PARP and the GSK3–HOXA9 axis can be a potential therapeutic approach to MLL rearranged leukaemia, which often confers a poor prognosis (*14*). Similar principle can also be applied to BRCA proficient cells. Cyclin D1 (CDK1) mediated phosphorylation of BRCA1 is essential for efficient DNA repair foci formation (*29*). Application of CDK1 inhibitor supressed HR and induced PARPi sensitivity in non–small-cell-lung cancer both *in vitro* and *in vivo* (*29*).

On the other hand, there are also indications for the potential use of PARPi as a chemotherapy sensitizer in leukaemia, although the mechanisms are not well defined. Falzacappa et al. reported that the combination of PARPi, Rucaparib, and conventional chemotherapy agent, fluorouracil, was effective in killing AML cells *in vitro* and *in vivo* (*30*). Fluorouracil was shown to induced DNA damage and together with the repression of the DDR by PARPi, the combination resulted in a significant increase in DNA damage leading to cell cycle arrest and death (*30*). Similar observation was found using AML cell lines exposed to histone deacetylase (HDAC) inhibitors and PARPi (*31*). HDACs catalyse the removal of acetyl groups from histone and other non-histone proteins altering gene expression and protein stability/function (*32*). HDAC inhibitors were reported to sensitise cancer cells to DNA damaging therapies such as irradiation and various chemotherapeutics by altering chromatin structure and down-regulating HR genes (*33, 34*). Thus, it is perhaps unsurprising that HDACs was found to synergise with PARPi in AML cell lines *in vitro* leading to significant increase in γH2AX upon combined treatments (*31, 35*). Simultaneous targeting cancers cells with temozolomide and PARPi have been shown successfully *in vitro* and *in vivo* in a number of cancers including AML (*36-38*). Temolozolomide has limited clinical utility other than for neurological malignancies and melanoma. It alkylates or methylates DNA, which most often occurs at the N-7 or O-6 positions of guanine residues. The excision of these N-methylpurines generates SSBs. PARP inactivation potentiates the effects of

temolozomide by inhibiting repair of these SSBs via BER. Under the same paradigm, DNA methyltransferases (DNMT) inhibitors (DNMTi) including 5-azacytidine and 5-aza-2'-deoxycytidine, have been reported to synergise with PARPi, olaparib (*39*). While the therapeutic mechanism of DNMT inhibitors in myelodysplastic syndrome (MDS) and AML is thought to be in part mediated by their DNA demethylation activity resulting in reactivation of silenced tumour suppressor genes (*40*) and induction of dsRNAs derived from endogenous retroviral elements that triggers interferon-dependent immune checkpoint (*41*, *42*), Orta et al. showed that BER was crucial for recognizing and repairing DNA lesions induced by DNMTi. BER deficient cells were sensitive to 5-azacytidine and displayed an increased amount of DNA single and double-strand breaks. PARP inhibition prevented recruitment of XRCC1 to the damage sites and therefore compromised BER. Combining 5-azacytidine and olaparib was found to cause synthetic lethality in a number of AML cell lines suggesting that PARP inhibitors can be used in combination with 5-azacytidine to improve treatment of MDS and AML patients.

Conclusions

PARPi alone or in combination with other treatments clearly exhibit various efficacies in targeting different subsets of leukaemia. Although the majority of the trials focus on the use of PARPi in solids tumours with BRCA mutations, several clinical trials are currently underway investigating the efficacy of PARPi in leukaemia (Table 1), where BRCA mutations are rare, which may in part explain only a limited number of PARPi clinical trials in AML. The major challenge of using PARPi in AML may come down to identifying reliable biomarkers to predict the treatment responses, which are largely determined by the driver mutations in leukaemia cells. By dissecting the molecular and transcriptional functions of these driver mutations in AML, we and others have revealed that PARPi can be particularly effective for treatment of leukaemia induced by certain oncogenic transcription factors (such as AML1-ETO and PML-RARα), which are classically intractable targets. PARPi can also be used in combination with GSK3i, chemotherapy or DNMTi to target MLL rearranged or other leukaemias. However, given the heterogeneity of the disease with patients carrying various additional cooperative mutations, it is likely that degree of treatment response to PARPi will vary between patients and within the tumour itself. In addition, some mutations may have opposing impacts on DDR, which are likely context dependent. For

example, FLT3-ITD, frequently found in AML has been reported to both induce DNA damages by inducing production of radical oxygen species (*8*) and promote HR via increased expression of HR genes (*43, 44*). It is critical to determine empirically the mechanisms and impacts of these cooperative mutations on PARPi sensitivity in AML patients. On the other hand, it is clear that PARPs have other diverse molecular functions beyond DDR that may also be critical for cancer survival and the observed synthetic lethality. A better understanding of the biological function of PARPs, cancer-driver mutations and their potential interactions is critical for designing better and effective cancer therapeutic strategies.

Acknowledgements

This work is supported by Bloodwise, Cancer Research UK and Kay Kendall Leukaemia Fund.

Finacial interetest

The authors declare no competing financial interest.

Reference

1. M. Rouleau, A. Patel, M. J. Hendzel, S. H. Kaufmann, G. G. Poirier, PARP inhibition: PARP1 and beyond. *Nat Rev Cancer* **10**, 293-301 (2010).
2. C. J. Lord, A. Ashworth, The DNA damage response and cancer therapy. *Nature* **481**, 287-294 (2012).
3. H. E. Bryant *et al.*, Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. *Nature* **434**, 913-917 (2005).
4. H. Farmer *et al.*, Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. *Nature* **434**, 917-921 (2005).
5. S. B. De Lorenzo, A. G. Patel, R. M. Hurley, S. H. Kaufmann, The Elephant and the Blind Men: Making Sense of PARP Inhibitors in Homologous Recombination Deficient Tumor Cells. *Front Oncol* **3**, 228 (2013).
6. T. Helleday, The underlying mechanism for the PARP and BRCA synthetic lethality: clearing up the misunderstandings. *Mol Oncol* **5**, 387-393 (2011).
7. N. McCabe *et al.*, Deficiency in the repair of DNA damage by homologous recombination and sensitivity to poly(ADP-ribose) polymerase inhibition. *Cancer Res* **66**, 8109-8115 (2006).
8. M. T. Esposito, C. W. So, DNA damage accumulation and repair defects in acute myeloid leukemia: implications for pathogenesis, disease progression, and chemotherapy resistance. *Chromosoma* **123**, 545-561 (2014).
9. C. Bassi *et al.*, Nuclear PTEN controls DNA repair and sensitivity to genotoxic stress. *Science* **341**, 395-399 (2013).

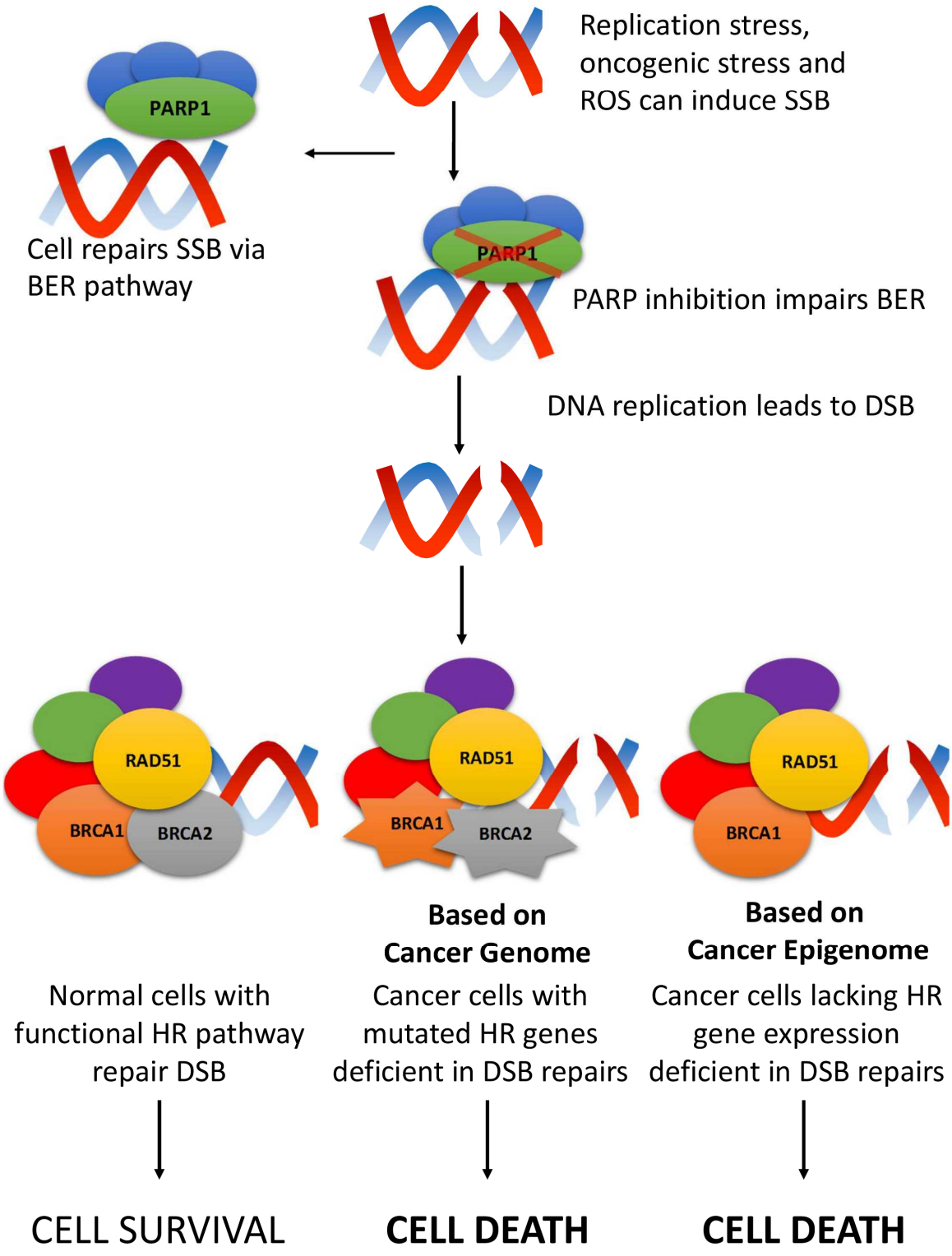
10. B. B. Zeisig, A. G. Kulasekararaj, G. J. Mufti, C. W. So, SnapShot: Acute myeloid leukemia. *Cancer Cell* **22**, 698-698 e691 (2012).
11. M. Alcalay *et al.*, Acute myeloid leukemia fusion proteins deregulate genes involved in stem cell maintenance and DNA repair. *J Clin Invest* **112**, 1751-1761 (2003).
12. O. Krejci *et al.*, p53 signaling in response to increased DNA damage sensitizes AML1-ETO cells to stress-induced death. *Blood* **111**, 2190-2199 (2008).
13. V. J. Forster *et al.*, The leukemia-associated RUNX1/ETO oncoprotein confers a mutator phenotype. *Leukemia* **30**, 250-253 (2016).
14. M. T. Esposito *et al.*, Synthetic lethal targeting of oncogenic transcription factors in acute leukemia by PARP inhibitors. *Nat Med* **21**, 1481-1490 (2015).
15. V. J. Forster *et al.*, The leukemia-associated RUNX1/ETO oncoprotein confers a mutator phenotype. *Leukemia* **30**, 251-254 (2016).
16. I. Casorelli *et al.*, Identification of a molecular signature for leukemic promyelocytes and their normal counterparts: Focus on DNA repair genes. *Leukemia* **20**, 1978-1988 (2006).
17. S. Zhong *et al.*, A role for PML and the nuclear body in genomic stability. *Oncogene* **18**, 7941-7947 (1999).
18. S. Boichuk, L. Hu, K. Makielski, P. P. Pandolfi, O. V. Gjoerup, Functional connection between Rad51 and PML in homology-directed repair. *PLoS One* **6**, e25814 (2011).
19. M. S. Song *et al.*, The deubiquitinylation and localization of PTEN are regulated by a HAUSP-PML network. *Nature* **455**, 813-817 (2008).
20. C. Q. Wang *et al.*, Disruption of Runx1 and Runx3 leads to bone marrow failure and leukemia predisposition due to transcriptional and DNA repair defects. *Cell Rep* **8**, 767-782 (2014).
21. C. Peng *et al.*, PTEN is a tumor suppressor in CML stem cells and BCR-ABL-induced leukemias in mice. *Blood* **115**, 626-635 (2010).
22. O. H. Yilmaz *et al.*, Pten dependence distinguishes haematopoietic stem cells from leukaemia-initiating cells. *Nature* **441**, 475-482 (2006).
23. J. Zhang *et al.*, PTEN maintains haematopoietic stem cells and acts in lineage choice and leukaemia prevention. *Nature* **441**, 518-522 (2006).
24. W. H. Shen *et al.*, Essential role for nuclear PTEN in maintaining chromosomal integrity. *Cell* **128**, 157-170 (2007).
25. K. J. Dedes *et al.*, PTEN deficiency in endometrioid endometrial adenocarcinomas predicts sensitivity to PARP inhibitors. *Sci Transl Med* **2**, 53ra75 (2010).
26. A. M. Mendes-Pereira *et al.*, Synthetic lethal targeting of PTEN mutant cells with PARP inhibitors. *EMBO Mol Med* **1**, 315-322 (2009).
27. I. Faraoni *et al.*, BRCA1, PARP1 and gammaH2AX in acute myeloid leukemia: Role as biomarkers of response to the PARP inhibitor olaparib. *Biochim Biophys Acta* **1852**, 462-472 (2015).
28. P. Moskwa *et al.*, miR-182-mediated downregulation of BRCA1 impacts DNA repair and sensitivity to PARP inhibitors. *Mol Cell* **41**, 210-220 (2011).
29. N. Johnson *et al.*, Compromised CDK1 activity sensitizes BRCA-proficient cancers to PARP inhibition. *Nat Med* **17**, 875-882 (2011).
30. M. V. Falzacappa *et al.*, The Combination of the PARP Inhibitor Rucaparib and 5FU Is an Effective Strategy for Treating Acute Leukemias. *Mol Cancer Ther* **14**, 889-898 (2015).
31. T. J. Gaymes *et al.*, Histone deacetylase inhibitors (HDI) cause DNA damage in leukemia cells: a mechanism for leukemia-specific HDI-dependent apoptosis? *Mol Cancer Res* **4**, 563-573 (2006).

32. K. T. Thurn, S. Thomas, A. Moore, P. N. Munster, Rational therapeutic combinations with histone deacetylase inhibitors for the treatment of cancer. *Future Oncol* **7**, 263-283 (2011).
33. S. K. Kachhap *et al.*, Downregulation of homologous recombination DNA repair genes by HDAC inhibition in prostate cancer is mediated through the E2F1 transcription factor. *PLoS One* **5**, e11208 (2010).
34. S. Adimoolam *et al.*, HDAC inhibitor PCI-24781 decreases RAD51 expression and inhibits homologous recombination. *Proc Natl Acad Sci U S A* **104**, 19482-19487 (2007).
35. T. J. Gaymes *et al.*, Inhibitors of poly ADP-ribose polymerase (PARP) induce apoptosis of myeloid leukemic cells: potential for therapy of myeloid leukemia and myelodysplastic syndromes. *Haematologica* **94**, 638-646 (2009).
36. T. J. Gaymes *et al.*, Microsatellite instability induced mutations in DNA repair genes CtIP and MRE11 confer hypersensitivity to poly (ADP-ribose) polymerase inhibitors in myeloid malignancies. *Haematologica* **98**, 1397-1406 (2013).
37. M. Javle, N. J. Curtin, The potential for poly (ADP-ribose) polymerase inhibitors in cancer therapy. *Ther Adv Med Oncol* **3**, 257-267 (2011).
38. T. M. Horton *et al.*, Poly(ADP-ribose) polymerase inhibitor ABT-888 potentiates the cytotoxic activity of temozolomide in leukemia cells: influence of mismatch repair status and O6-methylguanine-DNA methyltransferase activity. *Mol Cancer Ther* **8**, 2232-2242 (2009).
39. M. L. Orta *et al.*, The PARP inhibitor Olaparib disrupts base excision repair of 5-aza-2'-deoxycytidine lesions. *Nucleic Acids Res* **42**, 9108-9120 (2014).
40. J. P. Issa *et al.*, Phase 1 study of low-dose prolonged exposure schedules of the hypomethylating agent 5-aza-2'-deoxycytidine (decitabine) in hematopoietic malignancies. *Blood* **103**, 1635-1640 (2004).
41. D. Roulois *et al.*, DNA-Demethylating Agents Target Colorectal Cancer Cells by Inducing Viral Mimicry by Endogenous Transcripts. *Cell* **162**, 961-973 (2015).
42. K. B. Chiappinelli *et al.*, Inhibiting DNA Methylation Causes an Interferon Response in Cancer via dsRNA Including Endogenous Retroviruses. *Cell* **162**, 974-986 (2015).
43. K. Bagrintseva *et al.*, FLT3-ITD-TKD dual mutants associated with AML confer resistance to FLT3 PTK inhibitors and cytotoxic agents by overexpression of Bcl-x(L). *Blood* **105**, 3679-3685 (2005).
44. C. H. Seedhouse *et al.*, DNA repair contributes to the drug-resistant phenotype of primary acute myeloid leukaemia cells with FLT3 internal tandem duplications and is reversed by the FLT3 inhibitor PKC412. *Leukemia* **20**, 2130-2136 (2006).

Figure 1: Schematics of applying synthetic lethality in AML

Reactive oxygen species (ROS) or replication stress causes DNA single-strand breaks (SSBs) that are normally repaired by base excision repair (BER). PARP inhibitors block BER pathway, leading SSBs to become double-strand breaks (DSBs) as DNA polymerase moves along the replication forks. In normal cells, homologous recombination can repair these breaks. However, cancer cells with mutations or transcriptional repression of HR genes (i.e.

BRCA1 or BRCA2) are unable to efficiently repair these damages leading to genomic instability and eventual cell death.


Replication stress, oncogenic stress and ROS can induce SSB
PARP1
Cell repairs SSB via BER pathway
PARP1
PARP inhibition impairs BER
DNA replication leads to DSB
RAD51
BRCA1
BRCA2
RAD51
BRCA1
BRCA2
RAD51
BRCA1
Based on Cancer Genome
Based on Cancer Epigenome
Normal cells with functional HR pathway repair DSB
Cancer cells with mutated HR genes deficient in DSB repairs
Cancer cells lacking HR gene expression deficient in DSB repairs
CELL SURVIVAL
CELL DEATH
CELL DEATH

Highlights:

- Synthetic lethal targeting of cancer genomes by PARP inhibitors (PARPi)
- Targeting aberrant transcription programmes by PARPi-induced synthetic lethality
- Potential use of PARPi as monotherapy in AML
- PARPi in combination with other agents in AML