

Claims

1. A method of treating an HR deficient cancer comprising;
5 administering a PARP inhibitor to an individual in need thereof and reducing 2'-deoxynucleoside 5'-phosphate N-hydrolase 1 (DNPH1) activity in the individual
2. A method of sensitising a HR deficient cancer in an individual to treatment with a PARP inhibitor comprising;
10 reducing DNPH1 activity in the individual,
wherein said reducing sensitises the HR deficient cancer to treatment with the PARP inhibitor .
3. A method of sensitising a HR deficient cancer in an individual to reduced or deficient 2'-deoxynucleoside 5'-phosphate N-hydrolase 1 (DNPH1) expression or activity comprising;
15 administering a PARP inhibitor to the individual,
wherein said administering sensitises the HR deficient cancer to reduced or deficient 2'-deoxynucleoside 5'-phosphate N-hydrolase 1 (DNPH1) expression or activity.
4. A method of treating an HR deficient cancer comprising;
20 administering a combination of PARP inhibitor and a 5-modified-2'-deoxypyrimidine nucleoside or to an individual in need thereof.
5. A method of sensitising a HR deficient cancer in an individual to treatment with a PARP inhibitor comprising;
25 administering a 5-modified-2'-deoxypyrimidine nucleoside to the individual,
wherein said administering sensitises the HR deficient cancer to treatment with the PARP inhibitor
6. A method of sensitising a HR deficient cancer in an individual to treatment with a 5-modified-2'-deoxypyrimidine nucleoside comprising;
30 administering a PARP inhibitor to the individual,
wherein said administering sensitises the HR deficient cancer to treatment with a 5-modified-2'-deoxypyrimidine nucleoside.
7. A method of treating an HR deficient cancer comprising;
35 administering a 5-modified-2'-deoxypyrimidine nucleoside to an individual in need thereof and reducing DNPH1 activity in the individual
8. A method of sensitising a HR deficient cancer in an individual to treatment with a 5-modified-2'-deoxypyrimidine nucleoside comprising;
40 reducing DNPH1 activity in the individual,
wherein said reducing sensitises the HR deficient cancer to treatment with the a 5-modified-2'-deoxypyrimidine nucleoside.

9. A method of sensitising a HR deficient cancer in an individual to reduced 2'-deoxynucleoside 5'-phosphate N-hydrolase 1 (DNPH1) expression or activity comprising;
5 administering a 5-modified-2'-deoxypyrimidine nucleoside to the individual,
wherein said administering sensitises the HR deficient cancer to reduced or deficient 2'-deoxynucleoside 5'-phosphate N-hydrolase 1 (DNPH1) expression or activity.
10. A method according to any one of claims 7 to 9 wherein the HR deficient cancer is resistant to
10 treatment with a PARP inhibitor.
11. A method of treating an HR deficient cancer comprising;
administering a PARP inhibitor and a 5-modified-2'-deoxypyrimidine nucleoside to an individual in
need thereof and reducing DNPH1 activity in the individual
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12. A method of sensitising a HR deficient cancer in an individual to treatment with a PARP inhibitor
comprising;
administering a 5-modified-2'-deoxypyrimidine nucleoside to the individual and reducing DNPH1
activity in the individual,
20 wherein said administering and reducing sensitises the HR deficient cancer to treatment with the
PARP inhibitor .
13. A method of ameliorating toxicity in an organ or tissue of an individual undergoing treatment with a
PARP inhibitor comprising;
25 selectively reducing SMUG1 activity in the organ or tissue of the individual.
14. A method according to claim 13 wherein the individual has an HR deficient cancer.
15. A method according to any one of the preceding claims wherein the PARP inhibitor is selected from
30 the group consisting of olaparib, rucaparib, niraparib, talazoparib, velaparib, pamiparib (BGB-290), CEP-
9722 (11-methoxy-2-((4-methylpiperazin-1-yl)methyl)-4,5,6,7-tetrahydro-1H-cyclopenta[a]pyrrolo[3,4-
c]carbazole-1,3(2H)-dione) and E7016 (10-((4-Hydroxypiperidin-1-yl)methyl)chromeno[4,3,2-de]phthalazin-
3(2H)-one).
- 35 16. A method according to any one of the preceding claims wherein the HR deficient cancer is deficient
in an HR gene selected from BRCA1, BRCA2, MUS81, RAD52, RAD51, RAD50, ATM/ATR, FANC, BARD1,
BRIP1, CHEK1, CHEK2, FAM175A, NBN, PALB2, MRE11A, NBS1, RBBP8 (CtIP), MRE11, RPA, MMR,
H2AX and TP53.
- 40 17. A method according to any one of the preceding claims wherein DNPH1 activity is reduced by
administering to the individual an agent which reduces DNPH1 activity.
18. A method according to claim 17 wherein the agent is a DNPH1 inhibitor.

19. A method according to claim 18 wherein the DNPH1 inhibitor is an organic compound having a molecular weight of 900 Da or less.
- 5 20. A method according to claim 19 wherein the DNPH1 inhibitor is a nucleoside or nucleotide analogue.
21. A method according to claim 20 wherein the DNPH1 inhibitor is N6BA or a pharmaceutically acceptable salt, solvate, or analogue thereof.
- 10 22. A method according to claim 17 wherein the agent is a suppressor nucleic acid that reduces expression of active DNPH1 polypeptide.
23. A method according to claim 22 wherein the suppressor nucleic acid is a siRNA or shRNA.
- 15 24. A method according to claim 23 wherein the suppressor nucleic acid comprises a nucleotide sequence at least 95% identical to a contiguous sequence of 15 to 40 nucleotides of SEQ ID NO: 2.
25. A method according to claim 22 wherein the suppressor nucleic acid is an antisense oligonucleotide.
- 20 26. A method according to claim 17 wherein the agent is a targeted nuclease that reduces expression of active DNPH1 polypeptide to the individual.
27. A method according to claim 26 wherein the targeted nuclease is a ZFN, TALEN or meganuclease that recognises a target sequence within the DNPH1 gene.
- 25 28. A method according to claim 26 wherein the targeted nuclease is a CRISPR associated nuclease, said CRISPR associated nuclease being administered in combination with a guide RNA that recognises a target sequence within the DNPH1 gene.
- 30 29. A method according to any one of claims 26-28 wherein the targeted nuclease cleaves genomic DNA at the target sequence of the DNPH1 gene, thereby causing a deletion or insertion which reduces expression of active DNPH1 polypeptide.
- 35 30. A method of screening for a compound useful in sensitising an HR deficient cancer in a patient to treatment with a PARP inhibitor or a 5-modified-2'-deoxypyrimidine nucleoside, the method comprising; determining the activity of DNPH1 in the presence or absence of a test compound, wherein a decrease in DNPH1 activity in the presence relative to the absence of the test compound is indicative that the test compound is a candidate compound for use in sensitising an HR deficient cancer in a patient to treatment with a PARP inhibitor.
- 40 31. A method of screening for a compound useful in sensitising an HR deficient cancer in a patient to treatment with a PARP inhibitor or a 5-modified-2'-deoxypyrimidine nucleoside, the method comprising;

determining the expression of DNPH1 in a mammalian cell in the presence or absence of a test compound,

wherein a decrease in DNPH1 expression in the presence relative to the absence of the test compound is indicative that the test compound is a candidate compound for use in sensitising an HR deficient cancer in a patient to treatment with a PARP inhibitor.

32. A method of screening for a compound useful in ameliorating toxicity in individual undergoing treatment with a PARP inhibitor comprising

determining the activity of SMUG1 in the presence or absence of a test compound,

wherein a decrease in SMUG1 activity in the presence relative to the absence of the test compound is indicative that the test compound is useful in ameliorating toxicity in individual undergoing treatment with a PARP inhibitor.

33. A method of screening for a compound useful in ameliorating toxicity in individual undergoing

treatment with a combination of a PARP inhibitor and a 5-modified-2'-deoxypyrimidine nucleoside comprising

determining the expression of SMUG1 in the presence or absence of a test compound,

wherein a decrease in SMUG1 expression in the presence relative to the absence of the test compound is indicative that the test compound is useful in ameliorating toxicity in individual undergoing treatment with a combination of a PARP inhibitor and a 5-modified-2'-deoxypyrimidine nucleoside.

34. A method according to claim 33 wherein the method further comprises determining the effect of the test compound on the expression or activity of SMUG1 in target organ or tissue relative to a non-target organ or tissue.

35. A method of predicting the response of an HR deficient cancer in an individual to a combination of active agents, selected from (i) a PARP inhibitor and an agent that reduces DNPH1 activity; (ii) a PARP inhibitor and a 5-modified-2'-deoxypyrimidine nucleoside, (iii) an agent that reduces DNPH1 activity and a 5-modified-2'-deoxypyrimidine nucleoside and (iv) a PARP inhibitor, an agent that reduces DNPH1 activity and a 5-modified-2'-deoxypyrimidine nucleoside, wherein the method comprises;

determining the expression of SMUG1 in a sample of HR deficient cancer cells obtained from the individual,

wherein a decrease in SMUG1 expression in the cancer cells relative to control cells may be indicative that the HR deficient cancer is insensitive or has reduced sensitivity to the combination of active agents and/or the individual is not responsive to the combination.

36. A method of predicting the response of an HR deficient cancer in an individual to a combination of active agents, selected from (i) a PARP inhibitor and an agent that reduces DNPH1 activity; (ii) a PARP inhibitor and a 5-modified-2'-deoxypyrimidine nucleoside, (iii) an agent that reduces DNPH1 activity and a 5-modified-2'-deoxypyrimidine nucleoside and (iv) a PARP inhibitor, an agent that reduces DNPH1 activity and a 5-modified-2'-deoxypyrimidine nucleoside, wherein the method comprises;

determining the expression of DNPH1 in a sample of HR deficient cancer cells obtained from the individual,

wherein a decrease in DNPH1 expression in the cancer cells relative to control cells may be indicative that the HR deficient cancer is sensitive or has increased sensitivity to the combination of active agents relative to control cells and/or the individual is responsive to the combination.

- 5 37. A method of predicting the response of an HR deficient cancer in an individual to a combination of active agents, selected from (i) a PARP inhibitor and an agent that reduces DNPH1 activity; (ii) a PARP inhibitor and a 5-modified-2'-deoxypyrimidine nucleoside, (iii) an agent that reduces DNPH1 activity and a 5-modified-2'-deoxypyrimidine nucleoside and (iv) a PARP inhibitor, an agent that reduces DNPH1 activity and a 5-modified-2'-deoxypyrimidine nucleoside, wherein the method comprises;
- 10 determining the intracellular concentration of hmdU in a sample of HR deficient cancer cells obtained from the individual,
- wherein an increase in intracellular concentration of hmdU in the cancer cells relative to control cells may be indicative that the HR deficient cancer is sensitive or has increased sensitivity to the combination of active agents relative to control cells and/or the individual is responsive to the combination.
- 15 38. A method of selecting an individual with an HR deficient cancer as likely to respond to therapy with a combination of active agents, selected from (i) a PARP inhibitor and an agent that reduces DNPH1 activity; (ii) a PARP inhibitor and a 5-modified-2'-deoxypyrimidine nucleoside, (iii) an agent that reduces DNPH1 activity and a 5-modified-2'-deoxypyrimidine nucleoside and (iv) a PARP inhibitor, an agent that reduces
- 20 DNPH1 activity and a 5-modified-2'-deoxypyrimidine nucleoside, wherein the method comprises;
- determining the expression of SMUG1 in a sample of HR deficient cancer cells obtained from the individual, and
- selecting the individual as likely to respond to therapy where the expression of SMUG1 is not decreased relative to control cells.
- 25 39. A method of selecting an individual with an HR deficient cancer as likely to respond to therapy with a combination of active agents, selected from (i) a PARP inhibitor and an agent that reduces DNPH1 activity; (ii) a PARP inhibitor and a 5-modified-2'-deoxypyrimidine nucleoside, (iii) an agent that reduces DNPH1 activity and a 5-modified-2'-deoxypyrimidine nucleoside and (iv) a PARP inhibitor, an agent that reduces
- 30 DNPH1 activity and a 5-modified-2'-deoxypyrimidine nucleoside, wherein the method comprises;
- determining the expression of DNPH1 in a sample of HR deficient cancer cells obtained from the individual, and
- selecting the individual as likely to respond to therapy where the expression of DNPH1 in the cancer cells is decreased relative to control cells.
- 35 40. A method of selecting an individual with an HR deficient cancer as likely to respond to therapy with a combination of active agents, selected from (i) a PARP inhibitor and an agent that reduces DNPH1 activity; (ii) a PARP inhibitor and a 5-modified-2'-deoxypyrimidine nucleoside, (iii) an agent that reduces DNPH1 activity and a 5-modified-2'-deoxypyrimidine nucleoside and (iv) a PARP inhibitor, an agent that reduces
- 40 DNPH1 activity and a 5-modified-2'-deoxypyrimidine nucleoside, wherein the method comprises;
- determining the intracellular concentration of hmdU in a sample of HR deficient cancer cells obtained from the individual, and

selecting the individual as likely to respond to therapy where the intracellular concentration of hmdU in the cancer cells is increased relative to control cells.

41. A method according to any of claims 38 to 40, wherein the method further comprises:
- 5 administering the combination of active agents to the individual selected as likely to respond to therapy.