Using functional genetic screens to understand and overcome PARP inhibitor resistance

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PROPOSITIONS ASSOCIATED WITH THE THESIS

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1. *Brca1-/-;p53-/-* and *Brca2-/-;p53-/-* mammary tumors may develop resistance to PARPi via distinct mechanisms that are independent of restoration of BRCA1/2 function.
   (Chapter 3 of this thesis)

2. Functional genetic screens are useful tools to identify new therapeutic targets to improve response to PARPi and revert resistance.
   (Chapter 4, 5 and 6 of this thesis)

3. PARPi resistance in 53BP1-deficient *Brca1-/-;p53-/-* cells can be reverted by reinstating post-replicative single-stranded DNA (ssDNA) gap exposure via depletion of DNA Ligase III (LIG3).
   (Chapter 4 of this thesis)

4. Identification of ssDNA gap exposure as a predictor of PARPi sensitivity creates new opportunities for designing combination therapies to improve response to PARPi.
   (Chapter 4 of this thesis)

5. Resistance to PARPi might be an inevitable consequence of the genomic instability of homologous recombination-deficient tumors.
   (Chapter 2 of this thesis)

6. The lack of prolonged responses in patients receiving PARPi points towards acquired mechanisms of resistance and highlights the need for rational combination treatment strategies that can achieve more durable disease control or complete tumor eradication.
   (Chapter 2 of this thesis)

7. The use of PARPi earlier in the treatment pathway might postpone the onset of PARPi resistance by avoiding the emergence of tumor subclones that have developed resistance to previous lines of treatment and that confer cross-resistance to PARPi.
   (Susana N. Banerjee and Christopher J. Lord, "First-line PARP inhibition in ovarian cancer — standard of care for all?", Nat. Rev. Clin. Oncol., 2020 and Simon Makin, "What's next for PARP inhibitors?", Nature, 2021)

8. Chromosomes A and B evidently contain genes, or groups of genes, which taken separately are not lethal to homozygotes raised at 16.5o but which become lethal when combined by crossing over. In view of their known origin by crossing over, chromosomes Nos. 18, 41, and 63 may be said to carry "synthetic lethals".
(Theodor Dobzhansky, "Genetics of natural populations; Xiii; Recombination and variability in populations of Drosophila pseudoobscura", Genetics, 1946)

9. To avoid resistance, one should consider the simultaneous exploitation of multiple distinct synthetic lethal interactions, for example, by combining targeting of a driver gene effect through synthetic lethality with inhibition of any synthetic rescue effects that would otherwise reverse the primary synthetic lethality.
(Alan Ashworth and Christopher J. Lord, Synthetic lethal therapies for cancer: what's next after PARP inhibitors?", Nat. Rev. Clin. Oncol., 2018)

10. Down to their innate molecular core, cancer cells are hyperactive, survival-endowed, scrappy, fecund, inventive copies of ourselves.
(Siddhartha Mukherjee, The Emperor of All Maladies: A Biography of Cancer)

11. The reward of the young scientist is the emotional thrill of being the first person in the history of the world to see something or to understand something.
(Cecilia Payne-Gaposchkin)

12. If a cluttered desk is a sign of a cluttered mind, of what, then, is an empty desk a sign?
(Albert Einstein)