Resistance to PARP inhibition by DNA damage response alterations in BRCA1/2-deficient tumors

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Propositions

1. PARP inhibitors do not completely inhibit the enzymatic function and allow residual PARP1/2 activity.
   (this thesis)

2. HR restoration cannot be achieved in the absence of BRCA2, indicating that BRCA2 – unlike BRCA1 – is indispensable for the HR-mediated repair. Thus, BRCA2-deficient tumors – unlike BRCA1-deficient tumors – cannot escape PARP inhibitor toxicity through the efficient repair of DNA double-strand breaks.
   (this thesis)

3. The molecular routes that cells employ to escape PARP inhibitor pressure might depend on the genetic context, the type of PARPi used, or both.
   (this thesis)

4. Drug resistance often comes at a fitness cost due to collateral or acquired vulnerabilities, which can be exploited to target resistant tumors.
   (this thesis)

5. Particularly interesting is the appearance of "synthetic" lethal and semi-lethal chromosomes, which arise through crossing over between chromosomes lacking these properties.
   (Theodore Dobzhansky, 'Recombination and variability in populations of Drosophila pseudoobscura.' Genetics 1946)

6. The poly(ADP-ribose) polymerase binds strongly to strand breaks in DNA and interferes with the access of repair enzymes to the damaged site. In the presence of inhibitors of poly(ADP-ribose) synthesis, such as 3-aminobenzamide, this situation may persist.
   (Masahiko S. Satoh & Tomas Lindahl, 'Role of poly(ADP-ribose) formation in DNA repair', Nature 1992)

7. Cancer is a disease of cell biology(…). Often the discoveries that have the most profound impact on cancer treatments emanate from basic research on model organisms, rather than from studies of highly complex human tumors.
   (Bruce Alberts, 'Redefining Cancer Research', Science 2009)

8. With holistic clarity of mechanism, cancer prognosis and treatment will become a rational science.
   (Douglas Hanahan & Robert A Weinberg, 'The Hallmarks of Cancer', Cell 2000)

9. I would rather have questions that can't be answered than answers that can't be questioned.
   (Richard Feynman)

10. A common mistake that people make when trying to design something completely foolproof is to underestimate the ingenuity of complete fools.
    (Douglas Adams, 'The Hitchhiker's Guide to the Galaxy')

11. Knowledge is only a rumor until it lives in the muscle.
    (proverb, the Asaro tribe of Indonesia and Papua New Guinea)

12. Killing good ideas is always a good idea.
    (advice I received during my PhD)