Cancer chess: molecular insights into PARP inhibitor resistance

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Propositions

Belonging to the thesis
'Cancer Chess: Molecular Insights into PARP Inhibitor Resistance'

1. The 53BP1 pathway enforces DSB end-protection through the action of ssDNA binding complexes. *(This thesis)*

2. DSB end-resection might be a reversible process and commitment to HR repair might be revoked by active fill-in. *(This thesis)*

3. The concept of collateral sensitivity can be demonstrated in PARPi resistant clones and may be exploitable through one-two punch approaches. *(This thesis)*

4. Personalized cancer therapy is a continuous process, the outcome of which may be improved by determining the molecular cause of resistance once it emerges. *(This thesis)*

5. Established GEM models can be refined through CRISPR/Cas9 technology to establish causal genotype-drug sensitivity relations. *(This thesis)*

6. The selective advantage of 53BP1 is an enigma because most of its described functions are not obviously beneficial. *(Zachary Mirman & Titia de Lange, '53BP1: a DSB escort', Genes Dev 2020)*

7. Mutational scars reflecting a HR repair defect are also apparent in tumors that do not have BRCA gene mutations, raising the possibility that the presence of such a "BRCAness scar" could be used to predict clinical responses to agents such as PARPi. *(Christopher J. Lord and Alan Ashworth, 'PARP inhibitors: Synthetic lethality in the clinic'. Science (2017) and Helen Davies et al., 'HRDetect is a predictor of BRCA1 and BRCA2 deficiency based on mutational signatures', Nat Med 2017)*

8. BRCA1-PARPi synthetic lethality is thought to derive from DSBs necessitating BRCA function in HR repair and/or replication fork protection, but toxicity may also derive from replication gaps. *(Ke Cong et al., 'Replication gaps are a key determinant of PARP inhibitor synthetic lethality with BRCA deficiency', Mol Cell 2021)*

9. The "co-clinical trial project" and "The Mouse Hospital" will streamline the progression from bench to bedside for experimental therapeutics or novel combinations of already approved drugs. *(Caterina Nardella et al., 'The APL paradigm and the "co-clinical trial" project', Cancer Discov 2011)*

10. Very often in oncology we try to go for the "Rambo" approach to the problem, but we may be better off going for the "Kasparov" one. *(Andrea Sottoriva, 'Controlling drug resistance with evolutionary principles', Nat Commun 2020)*

11. Logic will get you from A to B, imagination will take you everywhere. *(Albert Einstein)*

12. The greatest enemy of knowledge is not ignorance, it is the illusion of knowledge. *(Stephen Hawking)*