

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)