Targeted therapy for triple-negative breast cancer

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Propositions

1. Targeting receptor tyrosine kinase-mediated signal transduction is often confounded by functional redundancy and adaptive transcriptional responses following inhibition of these oncogenic receptors. **This thesis.**

2. Inhibition of cyclin dependent kinases that determine cell cycle progression and transcription can effectively kill triple-negative breast cancer (TNBC) cells that are otherwise resistant to Akt or MEK inhibitors. **This thesis.**

3. Co-treatment of EGFR inhibitor-resistant TNBC cells with EGFR inhibitors and a dual cdc7/CDK9 inhibitor obstructs DNA replication and RNA transcription resulting in G2/M cell cycle arrest and apoptosis. **This thesis.**

4. Treatment of TNBC cells with CDK9 inhibitors leads to transcriptional reprogramming of multiple oncogenic signalling pathways in TNBC cells and prevents expression of critical transcription factors essential for the proliferation of TNBC cells. **This thesis.**

5. Interruption of P-TEFb/CDK9-mediated transcription abrogates the resistance of TNBC cells to EGFR inhibition. **This thesis.**

6. MEK inhibition induces genome-wide modulation of chromatin in the form of *de novo* enhancer formation and remodelling, which can be effectively blocked by pharmacological targeting of P-TEFb complex members. **Zawitowski et al. Cancer Discov. 2017 7**(3)**:302-321.**

7. Cancer cells have a high demand for transcription and translation of anti-apoptotic proteins to resist programmed cell death, making transcriptional targeting of these proteins an attractive strategy for cancer treatment. **Liu et al. Int J Cancer. 2012 130**(5)**: 1216-26.**

8. A major challenge for the clinical development of highly selective agents against specific CDKs will be the establishment of companion diagnostics that will enable the selection of appropriate patient populations. **Asghar et al. Nat Rev Drug Discov. 2015 14**(2)**: 130-46.**

9. Improved *in vitro* and *in vivo* models that closely model all relevant tumour stroma interactions are needed to more accurately assess drug resistance, evaluate potential drug combinations and determine the therapeutic value of predictive biomarkers. **Holohan et al. Nat Rev Cancer. 2013 13(10): 714-26.**

10. Combining chemical biology, high-throughput screening, and in-depth transcriptomic analysis represents a potent strategy for the evaluation of novel targeted therapies and the identification of genes responsible for breast cancer cell growth.

11. Pre-clinical assessment of novel inhibitors is only fruitful and relevant in so far as these models recapitulate physiological reality and disease heterogeneity.

12. Conducting research is akin to learning a foreign language: obstacles are only overcome and progress is only made by dedication, preparation, practice, and interaction.