PARP inhibitor (PARPi) resistance is often associated with "revertant" mutations that restore BRCA1 or BRCA2 gene function. Drean and colleagues used CRISPR-Cas9 mutagenesis to model these reversion mutations, finding that PARPi treatment selects for revertant clones in a Darwinian fashion. The periodicity of PARPi administration and the pre-treatment frequency of revertant tumour cells also influenced the clonal composition of tumours after treatment, suggesting that these factors should be taken into consideration when using these drugs. Nevertheless, revertant tumour cells retained the sensitivity to clinical WEE1 kinase inhibitors found in non-reverted cells, suggesting that despite the restoration of some BRCA gene function, therapeutic vulnerabilities might exist in PARPi resistant patients.

**Cotargeting MEK and PDGFR/STAT3 Pathways to Treat PDAC**

Sahu et al. ______________ Page 1729

The KRAS-driven MEK pathway is one of the key drivers of pancreatic cancer, however direct targeting using MEK inhibitors is insufficient to provide effective clinical benefit due to drug resistance. Using high-throughput 2D and novel 3D drug screens, Sahu and colleagues identified the compensatory feedback loop via the PDGFRα/STAT3/S6 pathways as the mechanism of resistance to MEK inhibitors. Combination treatment with a MEK inhibitor and the multi-kinase inhibitor ponatinib was effective in targeting pancreatic cancer cells by inhibiting both the MEK pathway and the compensatory PDGFRα/STAT3/S6 pathways. These results reveal a combination drug treatment strategy that may be effective in pancreatic cancer.

**Tumor Vasculature-Targeted Enzyme Prodrug Therapy**

Krais et al. ______________ Page 1855

This study takes a unique two-step therapeutic approach for treating breast tumors. Here, Krais and colleagues first target an enzyme to the tumor blood vessels followed by the administration of a non-toxic substrate that is converted to a cytotoxic agent by the tumor-bound enzyme. Additionally, this tumor vasculature targeting is further capitalized upon by combination with rapamycin to counter hypoxia-induced prosurvival signaling and combination with cyclophosphamide to exploit the release of tumor antigens caused by the enzyme prodrug therapy. The therapeutic combinations synergistically improve outcomes and warrant further studies of enzyme prodrug systems for cancer therapy.

**A Potential Mechanism of ADC-induced Neutropenia**

Zhao et al. ______________ Page 1866

Neutropenia is a common adverse event in cancer patients treated with antibody-drug conjugates (ADCs). Zhao and colleagues used an in vitro assay in which hematopoietic stem cells were differentiated to neutrophils to show that ADCs containing protease cleavable linkers can contribute to neutropenia via extracellular cleavage mediated by serine proteases secreted by differentiating neutrophils in bone marrow. The inhibitory effect on differentiating neutrophils was not mediated by internalization of ADCs either by macropinocytosis or FcγRs. These results provide more insight into the mechanism of action for ADC-induced neutropenia and will be helpful in the design of new ADCs with better therapeutic index.