

## From the Editor

In the November issue of AJHO, the review on PARP inhibitors for ovarian cancer by Previs and colleagues illustrates two important and recurring themes in cancer biology and treatment. One is the concept of synthetic lethality – that is, knocking out more than one critical pathway that together can synergistically disable malignant cell growth



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and survival. The other tenet is the potential to target cancer pathways that involve multiple tumor types, but require proper selectivity of patients with a diverse set of cancers. DNA repair is a critical cellular pathway that is necessary due to the ongoing assault on our genome, which must replicate 3 billion base pairs with every cell division. These repair pathways are redundant (as are most critical processes), so knocking out more than one could make a big difference. In the laboratory, cells that are already double stranded DNA repair-deficient owing to a *BRCA* mutation are exquisitely sensitive to disruption of other pathways such as base excision repair with PARP inhibitors. The second theme applies in this situation because *BRCA*-deficient tumors also include some breast, prostate, pancreatic, and other tumors. Additionally, several other aberrations such as methylation of *BRCA 1* promoter, and mutations/alterations in other DNA repair pathway genes may also results in sensitivity to PARP inhibitors and indeed, testing of these drugs in diverse cancer types that exhibit DNA repair deficiency (sometimes termed homologous repair deficiency) is underway with varying degrees of success seen so far.

But this story is not as clean – this is highlighted nicely in the review article. The impact of PARP inhibitors in the clinic is not nearly as dramatic as in the laboratory – a common finding given that intratumoral diversity and host-tumor interactions are not mirrored in preclinical models. In the clinic, not all *BRCA*-deficient or mutant cancers are sensitive to PARP inhibitors even from the start, and those that are initially sensitive ultimately develop clinical resistance. One alarming resistance mechanism is the development of additional mutations that even repair the *BRCA 1* gene back to its wildtype version. Certainly other bypass pathways are also operative, and this is an area of active research, with pathways such as PI3K/mTOR, MET, Wee1 and others being targeted. In addition, *BRCA 1/2* and other DNA repair gene aberrations may have different biological manifestations across the range of tumor types – this is due to the fact that these cells may have an altogether different set of expressed genes that may affect the function of the DNA repair machinery and associated bypass pathways. This may limit the power of the new trend to conduct “basket” trials across multiple tumor types with common genomic aberrations – therefore, many of these basket trials are followed by cohort expansions for each tumor type to further understand tumor-specific biology and clinical outcomes. As pointed out in this article, more fundamental basic research and exploration of rational combinations are needed to tackle this problem even with these new and exciting drugs.

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