

P014 *Brca2* Deficiency in the Murine Small Intestine Leads to Exquisite Sensitivity to PARP Inhibition
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Individuals who inherit a germline mutation in one copy of the *BRCA2* gene have an increased risk of developing breast cancer. We have used a well-established CYP1A1-driven *Cre-LoxP* approach to conditionally delete *Brca2* within the crypt epithelium of the mouse small intestine, including stem cells. Loss of functional *Brca2* caused a p53-dependent sensitivity to spontaneous DNA damage and hypersensitivity to DNA cross-linking agents. By using mice which carry the *Rosa26R* reporter allele, we show that stem cells in which *Brca2* had been deleted are slowly but eventually removed from the tissue by the process of re-population. We also treated these *Brca2*-deficient mice with an inhibitor of PARP, an enzyme involved in the process of recognition and repair of single and double strand breaks in DNA. We found that the intestines of these mice were exquisitely sensitive to PARP inhibition and that the rate of tissue re-population was increased remarkably after such treatment. These results in our model *Brca2*-deficient system add weight to the argument that PARP inhibitors may play an important role against tumours in which functional BRCA2 is absent.