A TP53 Knockout system for oncology drug testing.

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Abstract: TP53 is one of the most frequently mutated genes in human cancers. The effects of TP53 mutation on sensitivity to FDA approved chemotherapies is incompletely described. We generated TP53 knockout derivatives of MCF7 breast cancer cells using CRISPR-Cas9 technology, and measured in vitro differences in sensitivity to 133 chemotherapeutic agents in the NCI Approved Oncology Drug Set, and 92 anti-cancer compounds in the Biolog phenotype drug array plates M11-M14. TP53 KO clones were confirmed by genomic analysis of the targeted region, and by demonstrating resistance to the MDM2 inhibitor Nutlin3A. We identified drugs that were less effective in MCF7 cells with TP53 deletion compared to wild type parental cells, such as olaparib, oxaliplatin, and thiotepa. We also observed compounds that were more effective against TP53 KO cells, compared to wild type parental cells, including 4'-demethyl epipodphyllotoxin, hydroxyurea, and fluorouracil. These results provide clues to novel combinatorial regimens to try in preclinical and clinical models to target TP53 mutant human breast cancers. In addition, the isogenic sets of cell lines created for this investigation will be valuable for testing novel therapeutics for p53-dependent effects.