Molecular Cancer Research

Highlights

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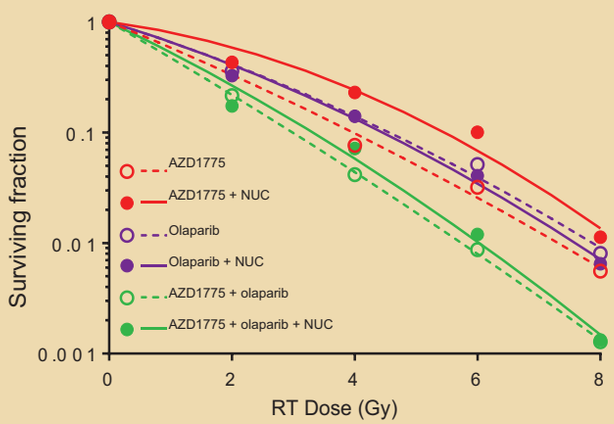
Selected Articles from This Issue



Radiosensitization by WEE1 and PARP Inhibition

Parsels *et al.*_____Page 222

Replication stress is emerging as an important mechanism for inhibitors of the DNA damage response. In this study, Parsels and colleagues defined the contribution of replication stress resulting from nucleotide depletion and PARP1 trapping to radiosensitization by the combination of WEE1 and PARP inhibitors, respectively, in KRAS-mutant NSCLC. They found that the enhanced radiosensitization from combined WEE1 and PARP inhibitors required PARP1 trapping, a dominant mechanism relative to nucleotide depletion. This study highlights the importance of replication stress to the therapeutic activity of WEE1 and PARP inhibitors and that PARP trapping potency is an important consideration in the choice of PARP inhibitor for combination therapy.

YAP1 Activator Suppresses Multiple Myeloma Cell Viability

Maruyama *et al.*_____Page 197

YAP1, a target of the Hippo pathway, is regarded as an oncogene in most human cancers. However, YAP1 co-operates with p73 in hematopoietic cells and plays a tumor suppressor role. Maruyama and colleagues conducted a novel transcription-based functional screening and identified candidate YAP1 activators (n = 47) from a small-molecule chemical compound library (n = 18,606). These compounds were characterized to determine whether this assay provides *bona fide* YAP1 activators. Importantly, one YAP1 activator induced apoptosis in human multiple myeloma and chronic myeloid leukemia cells. Hence, YAP1 activation may be useful at suppressing hematological cancers.

Autophagic Degradation of PD-L1 by a Sigma1 Modulator

Maher *et al.*_____Page 243

Immune checkpoint inhibitor antibodies that block PD-L1/PD-1 interactions are promising therapeutic agents; however, only a small percentage of cancer patients benefit from these agents. Small-molecule modulators of immune checkpoints and tumor microenvironment (TME) offer several advantages that complement current therapies, and may expand the population that responds to PD-L1/PD-1 targeted therapies. Herein, a novel mechanism is discovered by which small-molecule modulators of Sigma1, a unique ligand-operated integral membrane scaffolding protein, can be used to trigger PD-L1 degradation in cancer cells by selective autophagy. This posits Sigma1 modulators as novel therapeutic agents in PD-L1/PD-1 blockade strategies regulating tumor microenvironment.

Assigning Cancers to Effective Drugs with Big Data

Ding *et al.*_____Page 269

Precision oncology is currently limited in scope when using genomic biomarkers to guide prescription of molecularly targeted medications. In this study, Ding and colleagues applied state-of-the-art machine learning algorithms to create drug sensitivity prediction models using data from large pharmacogenomics studies, e.g., the Genomics of Drug Sensitivity in Cancer (GDSC) and Cancer Cell Line Encyclopedia (CCLE). The resulting models can accurately predict the efficacy of a wide array of molecularly targeted and non-specific chemotherapy drugs. Translated to the clinic, similar models have the potential to improve treatment outcomes for a significant population of patients currently receiving ineffective therapy.

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