LMP517, a Dual TOP1/TOP2 Inhibitor

Marzi *et al.* | Page 1589

Camptothecin-derived topoisomerase (TOP1) inhibitors have been approved for use in colorectal, ovarian, lung, and breast cancers. Indenoisoquinoline TOP1 inhibitors were designed to improve the half-life, reduce the resistance, and improve the side effects of camptothecin derivatives. Here, Marzi and colleagues provide additional improvements through introduction of a fluorine and removal of a methoxy group to generate LMP517. LMP517 shows dual activity against TOP1 and TOP2 and has selective activity against TDP1-deficient and Ku70-defective cells. LMP517 induced DNA damage at nanomolar concentrations in non-replicating G1 cells. Taken together, their results underline the potential clinical development of LMP517 for topoisomerase inhibition.

CS-1 Antibody Drug Conjugate Activity and Tolerability

Chen *et al.* | Page 1649

The surface glycoprotein CS-1 is highly expressed in multiple myeloma (MM) and is the target of the FDA-approved antibody elotuzumab. Despite the promise of CS-1 as a drug target, the single agent efficacy of elotuzumab remains modest. To combat this, Chen and colleagues generate a CS-1-targeted antibody-drug conjugate carrying a tesirine payload. They demonstrate its anti-tumor activity in mouse models of MM and outline its pharmacokinetic profile in cynomolgus monkeys. Investigation into the toxicity profile of the antibody-drug conjugate led to the discovery of CS-1 expression on myeloid-erythroid lineage progenitor cells, which should be considered in the continued design of CS-1-targeting antibodies.

Acquired Resistance to XPO1 Inhibitors

Miyake *et al.* | Page 1727

Selinexor, a selective inhibitor of nuclear export (SINE), is approved for patients with refractory multiple myeloma. It is currently in clinical trials for multiple solid tumors; however, many develop adaptive resistance over time. Miyake and colleagues investigated the mechanism behind this resistance using SINE-resistant ovarian cancer cell lines. The NRG1/ERBB3 pathway was up-regulated in SINE-resistant cells; siRNA depletion of ERBB3 restored the anti-tumor effects of SINE in vitro and in vivo. Exogenous NRG1 decreased the anti-tumor effects of SINE in ovarian cancer cell lines with high ERBB3 expression, but not in those with low expression. The authors conclude that NRG1 and ERBB3 expression are potential biomarkers of response to SINE treatment as well as potential therapeutic targets for the treatment of SINE-resistant cancers.

MAPK Reporter Assay in Pediatric Low-grade Glioma Cells

Usta *et al.* | Page 1736

Pediatric low-grade gliomas exhibit aberrant activation of MAPK, most commonly due to KIAA1549:BRAF fusions and BRAF V600E or NF1 mutations. To facilitate the discovery of MAPK inhibitors for these diseases, Usta and colleagues developed pediatric glioma cell lines transfected with a firefly luciferase driven by the MAPK-responsive ELK-1-binding element. Braf fusion and BRAF V600E mutant cell lines were tested against a MAPKi library and synergistic combinations were identified. In specific, MEK, ERK, and RAF inhibitors were identified as potential combination therapies for BRAF fusion and BRAF V600E mutant pediatric low-grade gliomas.