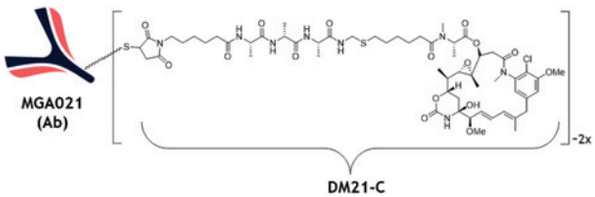
July 1, 2022 | Volume 21 | Number 7

MOLECULAR CANCER THERAPEUTICS
HIGHLIGHTS

Selected Articles from This Issue

IMGC936, an ADC Targeting ADAM9-expressing Tumors



Scribner *et al.* | Page 1047

Scribner and colleagues leveraged two platforms – an intact tumor cell immunization target discovery platform and a maytansine-based linker-drug platform – to identify cancer targets and develop ADCs against these targets. Antibodies to ADAM9 were generated with properties amenable to an ADC approach - among them, strong tumor-to-normal tissue binding differential and efficient internalization/processing by tumor cells. IMGC936, an ADC incorporating site-specific conjugation of DM21-C, a next-generation maytansine payload, was developed. IMGC936 exhibits potent antitumor activity in human CDX/PDX models and an acceptable safety profile in primates. The data supports initiation of a first-in-human study of IMGC936 in patients with solid tumors.

HJM-561 is a Potent and Oral Degrader of EGFR Triple Mutants

Du *et al.* | Page 1060

Active mutations in epidermal growth factor receptor (EGFR) are found in about 15% of Caucasian and 30–40% of Asian patients with advanced non-small-cell lung cancer (NSCLC). Currently there are no effective treatment options for NSCLC patients with osimertinib-resistant EGFR triple mutations. Here, Yong Du and coworkers report an orally bioavailable EGFR PROTAC, HJM-561, which selectively degrades EGFR C797S triple mutants with robust in vivo efficacy. This study provides a therapeutic option for treating osimertinib-resistant NSCLC patients and also suggests that targeted protein degradation is very promising to resolve drug resistance in cancer therapy.

TOP1-DNA Trapping and Therapeutics of Exatecan

Jo *et al.* | Page 1090

Tumor-targeted delivery cytotoxics are increasingly developed against various cancers. They require that: 1/the cytotoxic be potent but not highly toxic if released, and 2/delivery be tumor specific. Here, Jo and colleagues demonstrate that exatecan meets the first criterium by acting as a nano/picomolar topoisomerase I poison. They show that Schlafen 11 (SLFN11) expression, homologous recombination deficiency and combination with ATR inhibitors enhance the killing of cancer cells by exatecan. They also demonstrate that the potent anticancer activity of the exatecan-peptide prodrug conjugate CBX-12 is enhanced by combination with the ATR inhibitor ceralasertib in xenograft models.

Anti-mesothelin hYP218 Chimeric Antigen Receptor T cells

Tomar *et al.* | Page 1195

Mesothelin, a tumor antigen that is highly expressed in many solid tumors is an attractive target for CAR T cell therapy. However, these therapies have had limited efficacy in patients. Here, Tomar and colleagues have developed hYP218 CAR T cells, that bind the membrane-proximal region of mesothelin, with increased anti-tumor efficacy compared to identical CAR T cells that binds to the membrane-distal region of mesothelin. hYP218 CAR T cells were highly effective in multiple animal models, led to better tumor infiltration and persistence. These results support its clinical development for treating patients with mesothelin-expressing cancers.

doi: 10.1158/1535-7163.MCT-21-7-HI