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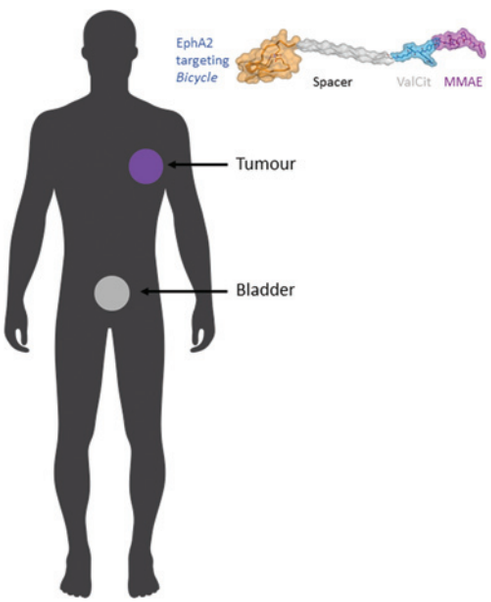
MOLECULAR CANCER THERAPEUTICS

# HIGHLIGHTS

**Selected Articles from This Issue**

## Targeted Delivery of MMAE Using Bicycle Molecules




**Bennett *et al.* | Page 1385**

The EphA2 receptor is an attractive target for oncology therapeutics. Here Bennett describes the preclinical profile of BT5528, a Bicycle peptide toxin-conjugate targeting EphA2. Bennett and colleagues show that BT5528 has rapid tumor uptake and fast renal elimination, providing persistent toxin levels in tumors without prolonged systemic exposure. The preclinical profile shows efficacy without bleeding toxicity, unlike a previous antibody conjugate targeting EphA2, which caused bleeding preclinically and in the clinic. The authors argue that this fast in, fast out kinetic profile offers the opportunity for a favorable balance of efficacy and toxicity in patients. Phase I trials are underway (NCT04180371).

## Pharmacology of *ESR1* Mutants in Breast Cancer

**Andreano *et al.* | Page 1395**

Mutations in the estrogen receptor (ER/*ESR1*) limit the response of metastatic breast cancer to aromatase inhibitors. It is also predicted that the most commonly occurring *ESR1* mutations would limit the use of selective estrogen receptor downregulators (SERDs) and selective estrogen receptor modulators (SERMs) when used as second-line therapy. Andreano and colleagues determined that resistance develops when mutant ERs are overexpressed relative to wild-type ERs. Furthermore, they found lasofoxifene, an SERM, was not affected by the mutant status. Their work suggests estrogen deprivation selects for ER mutants and resistance and underlines lasofoxifene as a viable therapeutic for patients with concerns for ER mutations.

## Synergistic Inhibition of NUT Carcinoma by NEO2734

**Morrison-Smith *et al.* | Page 1406**

NUT midline carcinoma (NMC) is a rare squamous carcinoma marked by the transcription of oncogenic genes by BRD4-NUT fusion and recruitment of p300 histone acetyltransferase. Morrison-Smith and colleagues demonstrate that inhibiting both p300 (GNE-781) and BET bromodomains (OTX015) effectively depleted MYC and inhibited NMC growth. Therefore, they employ a dual p300/BET bromodomain inhibitor, NEO2734, and demonstrate tumor regressions not seen in any other treatment *in vivo*. NEO2734 therefore represents a promising pre-clinical thrapeutic for NMC.

## Antitumor Properties of miR-3622b-5p in Ovarian Cancer

**Vernon *et al.* | Page 1506**

New solutions are urgently needed for ovarian cancers. Looking to find a new solution from antitumor miRNA molecules, Vernon and colleagues outline the profile of miR-3622b-5p. MiR-3622b-5p induces apoptosis through Bcl-xL and EGFR and prevented cell migration through targeting LIMK1 and NOTCH1. Therefore, they mimicked this antitumor profile using a combined EGFR inhibitor and BH3 mimetic in ovarian cancer cell lines and patient-derived organoids. By replicating the effects of an miRNA, the authors generate a new drug combination strategy in ovarian cancer.

Molecular Cancer Therapeutics

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*Mol Cancer Ther* 2020;19:1383.