Molecular Cancer Therapeutics **Highlights**

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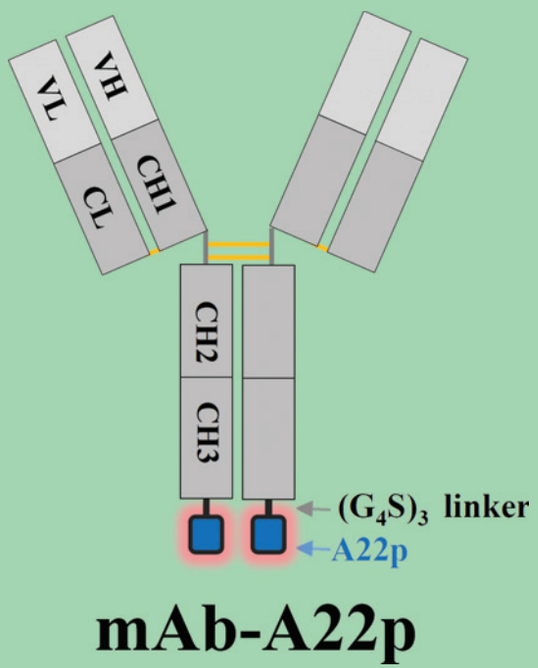
Selected Articles from This Issue



A New Antibody Format Showing Enhanced Tumor Penetration

Shin *et al.*_____Page 651

Poor localization and penetration of monoclonal antibodies (mAb) into solid tumors restricts their antitumor efficacy. To overcome these limits, Shin and colleagues designed a novel solid tumor–penetrating antibody format, mAb-A22p, by genetic fusion of high-affinity neuropilin-targeting A22p peptide to the C-terminus of the heavy chain of the conventional mAbs, such as anti-EGFR cetuximab and anti-Her2 trastuzumab. The mAb-A22p antibodies showed much better tumor homing, extravasation from the vessels, and tumor tissue penetration, resulting in more potent antitumor efficacy, compared with the parent mAbs. This study indicates that mAb-A22p is a superior format for solid tumor–targeting therapeutic antibodies.

Novel Selective Mcl-1 Inhibitor for Pancreatic Cancer Treatment

Abulwerdi and Liao *et al.*_Page 565

Mcl-1 represents an important survival factor for pancreatic cancer. In this study, Abulwerdi, Liao, and colleagues reported the preclinical data for a novel, selective small molecule Mcl-1 inhibitor, UMI-77, that targets the BH3-binding groove of Mcl-1. UMI-77 potently inhibits *in vitro* and *in vivo* pancreatic cancer growth by antagonizing Mcl-1 function and inducing Bax/Bak-dependent apoptosis. Western blot analysis in tumor remnants revealed enhancement of proapoptotic markers and significant decrease of survivin. These data provide evidence of Mcl-1 as a potential therapeutic target for pancreatic cancer and UMI-77 is currently being evaluated in combination with chemotherapy and radiotherapy.

A New Target for Overcoming Antimicrotubule Drug Resistance

Miao and Wu *et al.*_____Page 699

One of the major mechanisms underlying antimicrotubule drug (AMD) resistance involves acquired inactivation of the spindle assembly checkpoint (SAC). In this study, Miao, Wu, and colleagues report that synuclein gamma (SNCG), highly expressed in cancer cells but not in normal epithelium, is sufficient to induce AMD resistance in breast cancer through inhibiting the activity of spindle checkpoint kinase BubR1. SNCG-overexpressed cancer cells have a reduced ability to initiate and maintain proper mitotic arrest, which leads to AMD resistance by premature exit, before cells initiate apoptosis. These findings provide the basis for targeting SNCG in overcoming AMD resistance in cancer treatment.

Cancer-Associated CD43 Glycoforms as Target of Immunotherapy

Tuccillo and Palmieri *et al.*_Page 752

The UN1 monoclonal antibody (mAb) recognized CD43 glycoforms expressed in lymphoblastoid T-cell lines and solid tumors, and not in their normal counterpart. Here, Tuccillo, Palmieri, and colleagues demonstrated that UN1 mAb was endowed with ADCC activity *in vitro* and antitumor activity *in vivo*. By screening a phage-displayed random peptide library, they also identified the phagotope 2/165 as a mimotope of the UN1 antigen, which was able to elicit specific antibodies against the UN1/CD43 epitope in mice. These findings support the feasibility of using monoclonal antibodies to identify cancer-associated mimotopes and indicate the potential of cancer-associated CD43 as a target for immunotherapy.

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