Molecular Cancer Therapeutics Highlights

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Selected Articles from This Issue

Rational Combination Therapies for the Treatment of Cancer

Roller *et al.* _____ **Page 2505**

Molecular targeted therapies against signaling molecules active in cancer have shown incomplete and temporary clinical benefit when used as single agents. Roller and colleagues hypothesized that a functional chemical genetic screen could identify novel interactions between signaling inhibitors that would not be predicted based on the current understanding of signaling networks. Interestingly, the screen identified synergistic cytotoxicities that did not correlate with the *RAS* and *BRAF* mutational status. The authors uncovered novel functional drug combinations (including sorafenib, a multi-kinase inhibitor with activity against RAF, and diclofenac, a non-steroidal anti-inflammatory drug) and suggest that the underlying signaling networks that control responses to targeted agents can vary substantially depending on unexplored components of the cell genotype.

Inhibition of TGF-β Improves Anti-EGFR Antibody Therapy

Bedi *et al.* _____ **Page 2429**

EGF receptor (EGFR)–targeted monoclonal antibodies (mAb), such as cetuximab, execute their antitumor effect *in vivo* via blockade of receptor–ligand interactions and engagement of Fcg receptors on immune effector cells that trigger antibody-dependent cell-mediated cytotoxicity. Bedi and colleagues show that tumors counteract the *in vivo* antitumor activity of anti-EGFR mAbs by increasing tumor cell-autonomous expression of TGF-β and that TGF-β suppresses the expression of key molecular effectors of immune cell–mediated cytotoxicity. TGF-β is a key molecular determinant of the *de novo* and acquired resistance of cancers to EGFR-targeted mAbs, and provides a rationale for combinatorial targeting of TGF-β to improve anti-EGFR–specific antibody therapy of EGFR-expressing cancers.

Anti-CCR4 Antibody for Immunotherapy

Chang *et al.* _____ **Page 2451**

CC chemokine receptor 4, CCR4, is upregulated and is highly expressed in a large proportion of cutaneous T cell lymphoma (CTCL) and regulatory T cells (Tregs). To identify its antagonist antibody for cancer therapy, Chang and colleagues humanized and affinity maturated a mouse anti-CCR4 monoclonal antibody. This humanized antibody was highly specific to CCR4, exhibited the antagonist function to inhibit chemotaxis of Tregs, and enhanced therapeutic index in a CTCL xenograft model. The anti-CCR4 antibody additionally abrogates Treg function and activates proliferation of effector T cells. This multifunctional antibody may present a novel and promising cancer immunotherapy with immunomodulatory activity.

Stromal PDGFRα Targeting in Lung Cancer

Gerber *et al.* _____ **Page 2473**

In non-small cell lung cancer (NSCLC), platelet-derived growth factor receptor α (PDGFRα) is expressed frequently by stromal cells in the tumor microenvironment. However, previous research has focused largely on targeting tumor cell PDGFRα. To evaluate the effects of targeting tumor cell and stromal PDGFRα, Gerber and colleagues capitalized on xenograft modeling (human cancer cells, mouse stroma) and species-specific anti-PDGFRα monoclonal antibodies. Stromal PDGFRα inhibition attenuated tumor growth and enhanced the effect of chemotherapy in PDGFRα-negative NSCLC xenografts. These results suggest that inhibition of stromal PDGFRα may represent a means for enhancing control of lung cancer growth, independent of tumor cell PDGFRα expression.