Molecular Cancer Therapeutics Highlights

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Selected Articles from This Issue

PI3K/AKT Signaling and Resistance to HER2-Targeted Therapy

O'Brien *et al.* **Page 1489**

Resistance to HER2-targeted therapy continues to be a significant clinical problem principally due to a lack of predictive factors that consistently track with response. To address this issue, O'Brien and colleagues used multiple *in vitro* assays to comprehensively classify the trastuzumab and lapatinib responses of a large panel of breast cancer cell lines. Increased PI3K/AKT signaling was found to be common to trastuzumab resistance but not lapatinib resistance. Also, lapatinib retained activity in trastuzumab resistant cells via continued downregulation of PI3K/AKT signaling. These data suggest that targeting the PI3K/AKT pathway in addition to anti-HER2 therapy will improve patient responses.

Na,K-ATPase, a Novel EMT Biomarker for Cancer and Fibrosis

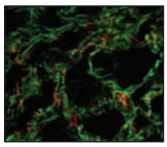
Rajasekaran *et al.* **Page 1515**

Although epithelial-to-mesenchymal transition (EMT) is involved in cancer and fibrosis, the disease outcomes are diverse. Common to both conditions is the loss of the polarized phenotype of epithelial cells and the gain of a mesenchymal phenotype. In this study, Rajasekaran and colleagues identified Na,K-ATPase β-subunit as a novel target of TGF-β that induces EMT in both cancer and fibrosis. They show that cells undergoing EMT and cancer cells that have a well-defined EMT have increased intracellular sodium levels due to dysregulation of Na,K-ATPase function and suggest that Na,K-ATPase is an early biomarker for EMT in cancer and fibrosis.

EMT and Resistance to Sunitinib

Hammers *et al.* **Page 1525**

The mechanisms of resistance to vascular endothelial cell growth factor receptor tyrosine kinase inhibitors (TKI) are poorly understood. To address this question, Hammers and colleagues obtained tumor specimens from a patient with clear cell renal cell carcinoma (CC-RCC) who progressed on sunitinib. Surprisingly, established mouse xenografts treated with sunitinib regained sensitivity to the drug. Histological examination of the original skin metastases revealed epithelial-to-mesenchymal-transition (EMT) while the xenografts showed reversion to the clear cell phenotype. These results suggest that reversible EMT may be associated with acquired resistance to TKIs in patients with CC-RCC and provide the rationale for novel therapeutic strategies.



ARQ 197: A Human c-Met Inhibitor with Antitumor Activity

Munshi *et al.* **Page 1544**

ARQ 197 is an orally available non-ATP competitive inhibitor of the c-Met receptor tyrosine kinase. The effects of ARQ 197 on c-Met driven cancer cell signal transduction pathways phenocopied siRNA knockdown of c-Met. The biochemical and antiproliferative potencies of ARQ 197 are within the same range, and ARQ 197 treatment inhibited growth of c-Met harboring human tumors in xenograft models. The biological characterization and impact of this novel drug candidate has begun to validate c-Met inhibition as an anticancer strategy across a broad range of human tumors.