Molecular Cancer Therapeutics

Highlights

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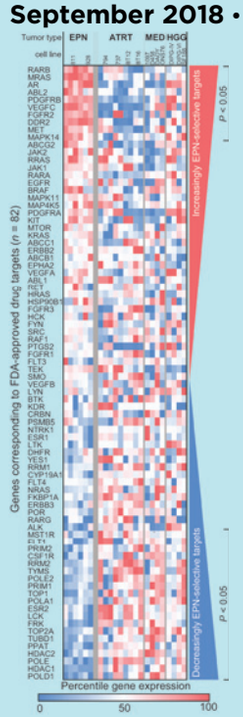
Selected Articles from This Issue



Ependymoma Drug Screen

Donson *et al.* Page 1984

Pediatric brain tumor ependymoma is incurable in approximately 50% of cases, and development of effective chemotherapy has been hindered by a lack of preclinical models. In this study, Donson and colleagues have used newly developed high-risk ependymoma cell lines for preclinical screening of FDA-approved oncology drugs. Three classes of drugs, fluorinated pyrimidines, retinoids and a subset of receptor tyrosine kinase inhibitors, demonstrated ependymoma-selective antitumor effect. Receptor tyrosine kinase inhibitor axitinib targeted PDGF receptor activity, a novel therapeutic susceptibility in ependymoma. These results will be informative in the design of upcoming ependymoma clinical trials.

Strategies to Address CAR Tonic Signaling

Ajina and Maher Page 1795

Chimeric antigen receptor (CAR) T-cell therapies are currently revolutionizing the care of patients with advanced hematologic malignancies. However, efficacy in patients with solid tumours has been lacklustre. One important consideration that remains poorly characterised is the propensity of these engineered proteins to signal in a constitutive, ligand-independent fashion. Moreover, chronic exposure to low-level endogenous ligand may similarly induce target-dependent tonic signalling with negative repercussions for CAR efficacy and persistence. Here, Ajina and Maher provide an in-depth review of the literature surrounding this phenomenon, contextualized through the lens of endogenous TCR signalling and posit strategies designed to minimize or co-opt tonic signalling to improve CAR T-cell function.

Targeting STAT3 with a Cyclic Decoy in NSCLC

Njatcha *et al.* Page 1917

STAT3, a transcription factor that is overactive in non-small cell lung cancer (NSCLC), has been difficult to inhibit clinically. As a point of convergence for receptor tyrosine kinase signaling, STAT3 is an important cancer target. Here, Njatcha and colleagues used a new approach to target STAT3 in NSCLC: a circular double-stranded DNA oligonucleotide containing the DNA sequence recognized by activated STAT3 proteins. This molecule acts as a DNA decoy by binding to activated STAT3 dimers, preventing them from initiating transcription of STAT3 target genes. The cyclic decoy showed robust anti-tumor activity in NSCLC models, providing strong support for further therapeutic development.

KDM6B Promotes PI3K Inhibitor Resistance

Wang and Lim *et al.* Page 1973

PI3K/AKT pathway is a promising target in luminal breast cancers. However, PI3K/AKT inhibitors show very limited clinical efficacy, and resistance often develops. Here, Wang, Lim and colleagues report a novel epigenetic mechanism of resistance to PI3K/AKT inhibitors in breast cancer. They show that H3K27me3 demethylase KDM6 promotes the expression of IGFBP5 leading to resistance to PI3K/AKT inhibitors, which could be reversed by KDM6B inhibitor, GSKJ4. Overexpression of KDM6B and IGFBP5 in luminal breast cancer are correlated with poorer disease outcomes. These results provide predictive biomarkers and a new paradigm in harnessing epigenetic therapeutics for overcoming resistance to PI3K/AKT inhibitors.

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