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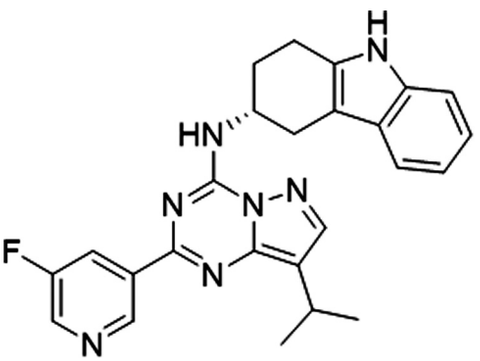
MOLECULAR CANCER THERAPEUTICS
HIGHLIGHTS

Selected Articles from This Issue

The AHR Inhibitor IK-175 Reverses Tumor Immune Suppression



McGovern *et al.* | Page 1261

The IDO1/TDO2-AHR pathway drives immunosuppressive tumor microenvironments and high pathway activity is correlated with poor prognosis in many cancer types. AHR is a transcription factor activated by kynurenine and other ligands and is an ideal therapeutic target for reversing the broad immunosuppressive activities mediated by this pathway. McGovern and colleagues introduce IK-175, a selective small molecule that inhibits AHR in vitro and in vivo. IK-175 inhibits tumor growth alone and combined with anti-PD-1 antibodies and reverses immune suppression and increases pro-inflammatory cytokines and effector immune cells in preclinical tumor models. These data provide rationale treating cancer patients with IK-175.

PLGA-Disulfiram Targets GBM *In Vitro* and *In Vivo*

Kannappan *et al.* | Page 1273

Glioblastoma (GBM) remains an incurable malignancy due to treatment resistance and inevitable recurrence. The hypoxic microenvironment in GBM promotes glioma stem cells via epithelial to mesenchymal transition, which are responsible for resistance, recurrence, and invasive nature of GBM. Here, Kannappan and colleagues have shown that Disulfiram, an anti-alcoholism drug effectively inhibits hypoxia induced stemness, resistance and migration/invasion potential of GBM by targeting NF-κB signalling which play a pivotal role in hypoxic regulatory network. PLGA encapsulated Disulfiram with extended half-life selectively targeted GBM in mouse xenograft models. Repurposing Disulfiram through novel drug delivery system offers new treatment options for GBM patients.

Ribociclib and Gemcitabine to Treat Medulloblastoma

Pribnow *et al.* | Page 1306

New therapeutic approaches are needed to address MYC-amplified Group 3 medulloblastoma, an aggressive pediatric tumor of the cerebellum. This cancer has a poor prognosis despite current therapies. Previous genomic profiling suggested that targeting the Cyclin/CDK axis could be effective therapeutically. However, CDK4/6 inhibitors are not effective alone and many drugs do not adequately penetrate the central nervous system (CNS). In this study, Pribnow and colleagues demonstrate that ribociclib, a CNS-penetrant CDK4/6 inhibitor, improves survival when combined with gemcitabine in preclinical orthotopic models. These translational findings hold promise for children with this type of medulloblastoma and may be applicable against other malignancies.

Nonclinical Efficacy and Safety CX-2029, an Anti-CD71 PDC

Singh *et al.* | Page 1326

Many potential cancer targets remain undruggable due to their expression in both normal and cancer tissue. A prime example of this is CD71, the transferrin receptor, which is highly expressed in multiple cancers, but is also widely expressed in normal cells because of its role in transporting iron into dividing cells. In this study, Singh and colleagues describe preclinical validation of CX-2029, a conditionally activated antibody drug conjugate (ADC) directed towards CD71 using Probody® technology, which is designed to result in preferential activation in the tumor microenvironment as a result of the activity of tumor-associated proteases to remove a protective mask. CX-2029 demonstrated promising tolerability and pharmacokinetics, with strong protection against hematopoietic toxicity in non-human primates compared to the unmasked control ADC. Additionally, CX-2029 treatment resulted in tumor growth inhibition in 28 of 34 mouse models of human cancer, including pancreatic, esophageal, non-small cell lung, head and neck cancer, and multiple others. CX-2029 is currently being evaluated in clinical trials in several tumor types.

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