Molecular Cancer Therapeutics

Highlights

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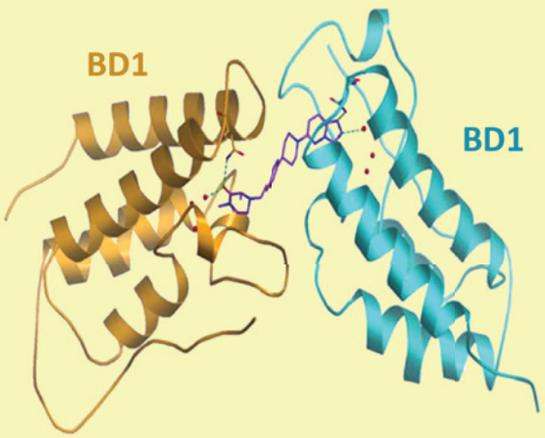
Selected Articles from This Issue



Bivalent Targeting of BRD4 by AZD5153

Rhyasen and Hattersley *et al.*_____Page 2563

Disrupting BRD4 activity through the use of small molecule probes has proven to be a widely effective preclinical anticancer strategy. To date, all reported BRD4 probes and clinical drug candidates operate through a monovalent binding mode. In this report, Rhyasen, Hattersley, and colleagues describe the pharmacology of AZD5153, a bivalent BRD4 inhibitor. The unique bivalent binding mode affords AZD5153 enhanced binding affinity, cell potency, and *in vivo* efficacy against hematologic cancer models. Targeting BRD4 through a bivalent binding mode therefore represents an attractive anticancer strategy.

Dual PI3K/BRD4 Inhibitor SF1126 Orthogonally Inhibits MYC in HCC

Singh, Joshi and Burgoyne *et al.*_____Page 2553

While most anticancer drugs have a single target, SF1126 inhibits two key signaling proteins within the liver cancer cell, PI3K and BRD4. Inhibition of PI3K enhances MYC degradation and BRD4 inhibition and prevents MYC transcription, providing a "first-in-class" approach to maximally block MYC-driven cancers. Singh, Joshi, Burgoyne and colleagues report this novel strategy of targeting two central signaling nodes with one agent that is antitumorigenic *in vitro* and *in vivo* and synergistic with the multikinase inhibitor Sorafenib. SF1126 is expected to enter HCC Phase I trials later this year.

Targeting Cytotoxics to Chondrosarcoma Proteoglycans: An Innovative Therapy

Peyrode and Weber *et al.*____Page 2575

Chondrosarcoma is a real challenge in orthopedic oncology and is notoriously chemoresistant. In this study, Peyrode, Weber, and colleagues develop an attractive proteoglycans-targeting chemotherapy approach using a quaternary ammonium conjugate of melphalan (Mel-QA). This work demonstrated the crucial role of the QA carrier for *in vitro* binding to aggrecan. *In vivo*, in chondrosarcoma-bearing rats, radiolabeled [^{3}H]-Mel-QA was shown to accumulate in tumor tissue respectively to melphalan, which was associated with tumor growth inhibition and improvement of the therapeutic index. These results open new perspectives in the therapeutic management of chondrosarcoma.

AC0010, a Novel EGFRmut Selective Inhibitor for NSCLC

Xu *et al.*_____Page 2586

AC0010 is a novel, irreversible, epidermal growth factor receptor (EGFR) inhibitor designed to overcome T790M-induced resistance in non–small cell lung cancer (NSCLC) patients. Preclinical studies demonstrate that AC0010 is a selective and potent inhibitor of EGFR activation and T790M mutations. A Phase 1 dose-escalation clinical study indicates that AC0010 is safe and effective in late-stage NSCLC patients. In this study, no pneumonitis, hyperglycemia, or grade 3 prolongation of the corrected QT interval event were observed. The preclinical and clinical evidence warranted further development of AC0010 as an alternative therapeutic agent for NSCLC patients who acquire resistance to first-generation EGFR TKIs.

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