Molecular Cancer Therapeutics

Highlights

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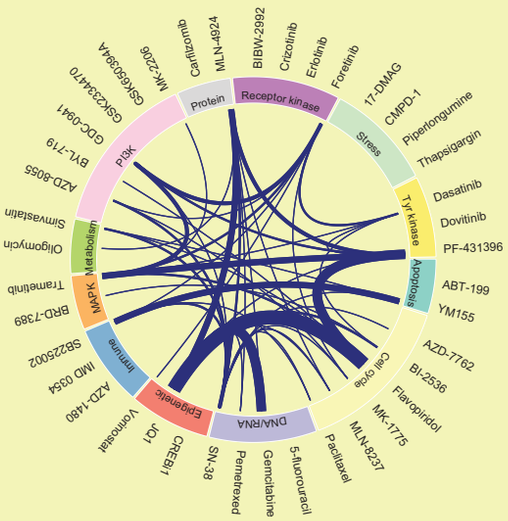
Selected Articles from This Issue



Combinatorial Drug Screening for Pancreatic Adenocarcinoma

Langdon *et al.* **Page 1041**

Pancreatic adenocarcinoma (PDAC), with dismal survival rates, is the fourth-leading cause of cancer death in the United States. Very few therapeutic options exist for PDAC patients. Langdon and colleagues describe a combinatorial drug screen to identify therapeutic regimens that can inhibit the growth of PDAC cells. One of several effective combinations, consisting of bromodomain inhibitor, JQ1, and neddylation inhibitor MLN-4924, super-additively inhibited the growth of PDAC cells and xenografts. Dysregulation of reactive oxygen species-induced DNA damage responses contributed to the impact of this combination. These, and other high-ranking combinations including US FDA-approved agents, offer some promise for control of PDAC.

Preclinical Characterization of Erdafitinib

Perera *et al.* **Page 1010**

Fibroblast growth factor receptors (FGFRs) are frequently activated by gene amplification, point mutation or chromosomal rearrangement in a variety of human cancers. FGFRs are recognized as an important oncogenic driver pathway for therapeutic intervention. In this study, Perera and colleagues report the discovery and pharmacologic characterization of erdafitinib (JNJ-42756493), a highly selective and potent pan-FGFR inhibitor. Erdafitinib demonstrated selective inhibition of FGFR-mediated signal transduction, proliferation and *in vivo* anti-tumor efficacy. These results support the ongoing clinical development of erdafitinib in malignancies and other disorders associated with constitutive FGFR activation.

Ibrutinib Antagonizes Paclitaxel Resistance

Zhang and Patel *et al.* **Page 1021**

Paclitaxel is a commonly used chemotherapeutic drug. However, resistance to paclitaxel has limited its clinical application. ABCB1 and ABCC10 are the major transporters causing efflux of paclitaxel, leading to paclitaxel resistance. Here, Zhang, Patel and colleagues report that ibrutinib antagonized the efflux function of the transporters. Ibrutinib effectively enhanced the anti-tumor efficacy of ABCB1 and ABCC10-overexpressing resistant tumors in mice. Molecular docking analysis revealed that ibrutinib interacts with ABCB1 within its large cavity in the transmembrane region. This study demonstrated that combination of ibrutinib with paclitaxel can reverse ABCB1- or ABCC10-mediated paclitaxel resistance that could be of great clinical interest.

AZD2811 Nanoparticle in AML

Floc'h *et al.* **Page 1031**

Acute myeloid leukemia (AML) is the most common leukemia diagnosed in adults and a disease of high unmet need with few therapies delivering durable benefit to patients. Floc'h and colleagues report activity of a highly potent and selective Aurora kinase B inhibitor AZD2811 formulated in a nanoparticle. The AZD2811 nanoparticle delivered durable responses in pre-clinical models of AML, as monotherapy and combined with chemotherapy, including targeting tumor cells resident in the bone marrow. Targeting Aurora B with the AZD2811 nanoparticle formulation has the potential to build on the promising clinical activity seen with cell cycle agents in AML.