Molecular Cancer Therapeutics

Highlights

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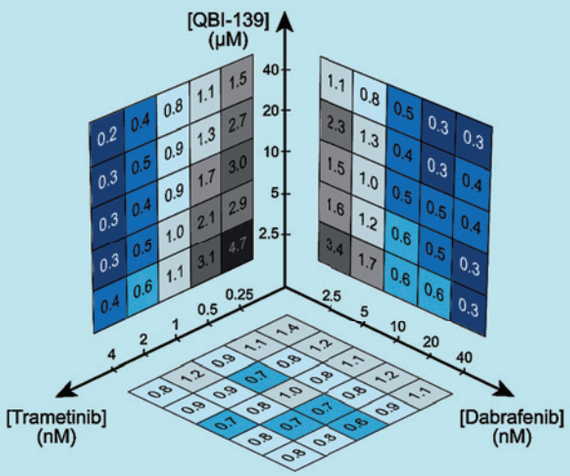
Selected Articles from This Issue



Synergism of a ribonuclease and ERK-pathway inhibitors

Hoang *et al.* Page 2622

The complex, highly interdependent nature of intracellular processes often hinders drug discovery. Hoang and colleagues report on a counter example by coupling the cytotoxicity of pancreatic-type ribonucleases (ptRNases) with extant cancer therapies. They discover that the ERK pathway is responsible for phosphorylating a cytosolic ribonuclease inhibitor protein and, thereby, confounding ptRNase cytotoxicity. ERK-pathway inhibitors undo this effect. The authors demonstrate this surprising synergy between seemingly unrelated processes by co-administering a clinical ptRNase (QBI-139) and KRAS/BRAF/MEK inhibitors to human lung cancer and melanoma cells. Such a combination could enhance the efficacy of kinase inhibitors and minimize drug resistance.

Co-targeting of MEK and CDK4/6 to treat pancreatic cancer

Maust *et al.* Page 2495

The high incidence of KRAS and CDKN2A mutations in pancreatic cancer supports dual targeting of MEK and CDK4/6 to treat this disease. Maust and colleagues show that the combination of trametinib and palbociclib elicits synergy and is highly active against two adenosquamous pancreatic cancer models. Sensitive tumors showed strong downregulation of cyclooxygenase-2 (COX-2) in response to co-targeting of MEK and CDK4/6. Furthermore, genetic manipulation of COX-2 expression blunted effectiveness of combination treatment. These results suggest a prognostic role for COX-2 in the identification of patients who might derive the greatest therapeutic benefit from this combination strategy.

AZD3514 enhances the anti-tumor effects of olaparib in breast cancer

Min *et al.* Page 2507

Targeting androgen receptor (AR) is an attractive therapeutic strategy for breast cancer (BC) and PARP inhibitors are effective for treating BC patients with germline BRCA 1/2 mutation. Min and colleagues explored the potential therapeutic effects of AR inhibitor AZD3514 and PARP inhibitor olaparib in BC cells. AZD3514 and olaparib co-treatment showed antitumor effect caused by compromised DNA damage repair activity. AR inhibition attenuated ATM-chk2 axis activity via downregulation of NKX3.1 mediated by TOPORS, subsequently led to enhance sensitivity to olaparib. The combination therapy of AR inhibitor with PARP inhibitor could expand the clinical usage of PARP inhibitor by inducing HRD-phenotype for AR-positive BC patients.

Delivery of NAMPT inhibitors using antibody-drug conjugates

Neumann *et al.* Page 2633

Antibody-drug conjugate (ADC) technology is limited by the diversity of payloads that are efficacious and tolerated in this delivery format. NAMPT is a critical enzyme in NAD biosynthesis, and inhibitors are potently cytotoxic due to disruption to energy metabolism. Neumann and colleagues describe the development of ADCs with NAMPT inhibitor payloads that deplete NAD in cells and induce tumor regression in xenograft models, while improving the tolerability of the drug class in rodent toxicology models. These findings introduce a new mechanism of action to the ADC field with promise to translate into efficacious and tolerated clinical agents.

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