Molecular Cancer Therapeutics

Highlights

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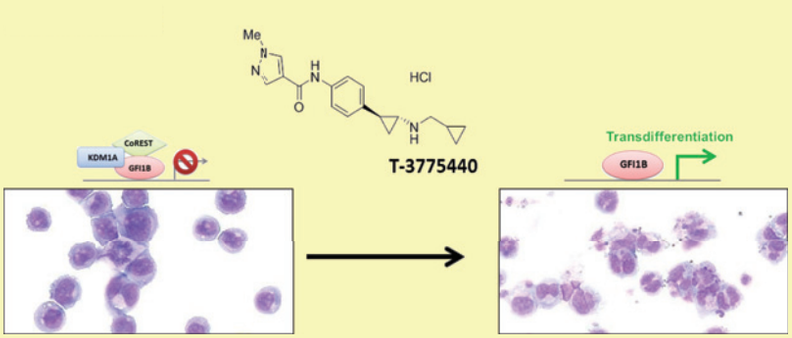
Selected Articles from This Issue



LSD1 Inhibitor Disrupts GFI1B-containing Complex in AML cells

Ishikawa *et al.*_____Page 273

The pharmacological inhibition of lysine specific demethylase 1 (LSD1, also known as KDM1A) has recently drawn attention as a novel therapeutic option against acute myeloid leukemia (AML). Here, Ishikawa, Gamo, and colleagues demonstrated that a novel irreversible LSD1 inhibitor, T-3775440, exhibited anti-leukemic efficacy in GFI1B-expressing acute erythroleukemia (AEL) and acute megakaryoblastic leukemia (AMKL) cells. T-3775440 exerts anti-AML effects through a mechanism involving disruption of the LSD1/GFI1B complex and consequent AML cell transdifferentiation. Given that several LSD1 inhibitors have entered clinical trials for treating patients with AML, these results provide new perspectives in the therapeutic strategy of AEL and AMKL.

Acquired Resistance Against Afatinib in Lung Cancer

Kobayashi *et al.*_____Page 357

The mechanism of acquired resistance against afatinib is still unclear. Here, Kobayashi and colleagues established a panel of resistant clones from Ba/F3 cells transduced with mutated EGFR genes (Del18, G719A, Del19 or L858R). Among 84 resistant clones, secondary C797S mutation was found in subsets of Del18, G719A or L858R but not in Del19 clones. A novel L792F was present in Del18 clones while the majority had a common T790M. Clones with C797S and L792F exhibit sensitivity to erlotinib and dacomitinib, respectively. In conclusion, afatinib resistance could be driven by L792F or C797S mutations and therefore testing novel combinations of EGFR-TKIs might benefit patients with these minor mutations.

Microdose-induced Drug-DNA Adducts as Biomarkers of Chemotherapy Resistance

Zimmermann *et al.*_____Page 376

Common cytotoxic chemotherapy regimens currently lack diagnostic tests that predict response. Zimmermann and colleagues demonstrated the feasibility of using microdose-induced drug-DNA adducts as predictive biomarkers of response to gemcitabine and cisplatin or carboplatin in a pilot clinical study and several mouse models of bladder cancer. Patients with the highest carboplatin-DNA adduct levels were responders, but not all responders had high adduct levels. In mice bearing patient-derived tumor xenografts, at least one of the drugs in the regimen had to induce high drug-DNA adduct levels or a synergistic increase in overall adducts to prompt a corresponding therapeutic response.

High-throughput Screening Seeking for Novel Combinations with Epigenetic Drugs

Raynal *et al.*_____Page 397

The potential of epigenetic drugs to synergize with other drugs against colon cancer cells remains to be uncovered. To identify new drug interactions, high-throughput screening was performed on cancer cells treated with DNA methylation or histone deacetylase inhibitors in combination with FDA-approved drug libraries. The screening model measured reporter gene expression level, as a surrogate for tumor suppressor gene reactivation. This study revealed new combinations of epigenetic drugs and FDA-approved drugs producing epigenetic synergy, which can be rapidly implemented into clinical trials against colon cancer.