



Acquired third-generation EGFR-TKI resistance mechanisms

Nakatani *et al.* _____ Page 112

Nakatani and colleagues aimed to identify novel resistance mechanisms to third-generation EGFR TKIs by establishing acquired resistance in afatinib-resistant lung adenocarcinoma cells carrying the exon 19 deletion/T790M mutation in EGFR. A significant KRAS amplification was observed in two osimertinib-resistant cell lines. In the first cell line, osimertinib resistance was not attenuated after osimertinib withdrawal for two months. In the second, sensitivity to osimertinib was restored after two months of osimertinib withdrawal; this effect involved EGFR and GRB2/SOS1 complex activation. Overall, the identified heterogeneous acquired resistance mechanism to third-generation EGFR TKIs will aid development of novel cancer treatment strategies.

PTC299 is a novel potent DHODH inhibitor

Cao *et al.* _____ Page 3

In-depth biological characterization demonstrates that PTC299 is a potent inhibitor of dihydroorotate dehydrogenase (DHODH), a rate limiting enzyme, for de-novo pyrimidine nucleotide synthesis. Unlike previously reported DHODH inhibitors, PTC299 is a more potent inhibitor of DHODH in isolated mitochondria than in purified enzyme suggesting mitochondrial membrane lipid engagement in the DHODH conformation *in situ* is required for optimal activity. PTC299 has broad and potent activity against hematological malignancies that have lower uridine salvage activity thus depending on de-novo pyrimidine synthesis. This study by Cao and colleagues suggests that PTC299 is a promising agent for treatment of blood cancers and will help to guide further clinical development.

Prognostic significance of ERR α in glioma

Zhang *et al.* _____ Page 173

Malignant glioma is an often fatal type of cancer. In this study, Zhang and colleagues found that high expression of the orphan nuclear receptor estrogen-related receptor alpha (ERR α) was associated with later stages of disease progression and worse clinical outcome in glioma patients treated with surgical resections. Further investigations confirmed that ERR α was involved in the carcinogenesis of glioma via the regulation of Wnt5a signal pathway *in vitro* and *in vivo*. The study reveals that ERR α has prognostic significance in glioma and targeting ERR α might provide reliable therapeutic strategy for the treatment for human glioma.

Multiplex 3D mapping of macromolecular drug distribution

Lee *et al.* _____ Page 213

There is increasing need for tools to track macromolecular drugs at high spatial and temporal resolution and in three dimensions within the tumor microenvironment, which is characterized by disorganized vasculature and cellular heterogeneity. Here, Lee and colleagues adapted Transparent Tissue Tomography (T3) as a new tool to enable 3D pharmacokinetics, measuring drug delivery to experimental tumors at cellular resolution. The authors used T3 to analyze perfusion, extravasation and penetration of anti-PD-L1 antibodies and measure binding to PD-L1 in the tumor microenvironment. These studies establish T3 as a new tool to accelerate development of macromolecular cancer drugs and nanomedicines.

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