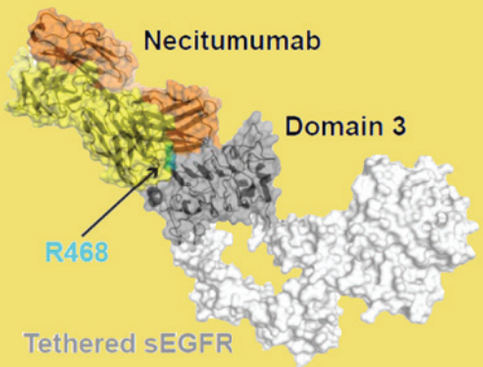
Molecular Cancer Therapeutics

Highlights

February 2018 • Volume 17 • Number 2

Selected Articles from This Issue



Necitumumab Blocks Cetuximab-Resistant, Mutated EGFR

Bagchi and Haidar *et al.* Page 521

In some colorectal cancer (CRC) patients who develop resistance to cetuximab, tumors have acquired somatic mutations that map to the cetuximab epitope, blocking antibody binding. Bagchi, Haidar and colleagues show that necitumumab, another FDA approved EGFR antibody, binds to and inhibits cetuximab resistant EGFR, despite sharing an almost identical epitope to cetuximab. Unlike cetuximab, necitumumab has a large paratope cavity that accommodates CRC-linked substitutions in EGFR, such as the commonly observed S468R (S492R including the signal peptide). A simple computational approach predicts which EGFR variants bind necitumumab. This work suggests that necitumumab may be effective in some cetuximab-resistant CRC cases.

A Novel YAP1 Inhibitor Overcomes Radiation Resistance in EAC

Song *et al.* Page 443

Esophageal adenocarcinoma (EAC) is inherently heterogeneous and often resistant to therapy. Hippo co-activator YAP1 is amplified in EAC and highly expressed. YAP1 confers cancer stem cell (CSC) properties, aggressive phenotype, and therapy resistance. Targeting YAP1 would be a novel therapeutic strategy but YAP1 inhibitors are currently lacking. In this issue, Song and colleagues report identification of CA3 as a potent YAP1 inhibitor. CA3 inhibited YAP1/Tead transcriptional activity and the growth of YAP1-high and radiation resistant EAC cells endowed with CSCs properties. When combined with fluorouracil, the therapeutic effects of CA3 were amplified both *in vitro* and *in vivo*.

Entrectinib is Effective Against *NTRK* Fusion-Positive AML

Smith *et al.* Page 455

TRK kinase activation by chromosomal rearrangement is an oncogenic driver in a small percentage of tumors across a wide range of histologies. Effective targeted therapy against TRK has had significant positive impact in these patients' lives. Building upon preclinical and clinical studies demonstrating entrectinib efficacy in TRK fusion-positive solid tumors, this report provides evidence of entrectinib efficacy in TRK fusion-positive AML models. This study has broad implications in hematologic malignancies, with *NTRK* fusions identified in ALL, CEL and MM. As molecular profiling increases in hematologic malignancies, it is increasingly important to investigate options for patients with rare but actionable alterations.

Novel Combination of Onapristone and Trametinib in Uterine Cancer

Huang and Hu *et al.* Page 464

The clinical use of progesterone receptor (PR)-targeted therapies is limited, in part, by the lack of biomarkers that predict response to PR-agonists or PR-antagonists. Understanding the molecular mechanisms of action will provide an advance in developing novel combination therapies for cancer patients. Huang, Hu and colleagues have identified that onapristone, a pure PR antagonist, inhibited nuclear translocation of ligand-dependent or EGF-induced phospho-PR (S294), while trametinib only inhibited nuclear translocation of EGF induced phospho-PR (S294). Moreover, the combination of onapristone and trametinib resulted in superior anti-tumor effects in uterine cancer models, highlighting that targeting MAPK-dependent PR activation with onapristone and trametinib may be worthy of further development.