
Précis: Sequencing of longitudinal biopsies from a patient with NRAS-mutant melanoma reveals a preexisting PI3KCAE545K mutation that increases S6K1 signaling to confer resistance to MEKi plus CDK4i.

See commentary, p. 532
See article, p. 568

In Vivo E2F Reporting Reveals Efficacious Schedules of MEK1/2–CDK4/6 Targeting and mTOR–S6 Resistance Mechanisms


Précis: Continuous MEK inhibition plus intermittent CDK4/6 inhibition achieves maximal antitumor activity with limited toxicity in melanoma mouse models, and mTORC inhibition may overcome acquired resistance.

See commentary, p. 532
See article, p. 556

Cross-Cohort Analysis Identifies a TEAD4–MYCN Positive Feedback Loop as the Core Regulatory Element of High-Risk Neuroblastoma


Précis: TEAD4 functions as a tumor subtype-specific master regulator in MYCN-amplified high-risk neuroblastoma and induces a core transcriptional module via positive-feedback interaction with MYCN.
Genomic and Functional Fidelity of Small Cell Lung Cancer Patient-Derived Xenografts 600
Précis: A strategy for the efficient development of SCLC PDX models from tumor biopsies and circulating tumor cells faithfully recapitulates the patient tumors and identifies biomarkers of response to chemotherapy.

HOXA9 Cooperates with Activated JAK/STAT Signaling to Drive Leukemia Development 616
Précis: HOXA9 upregulation is associated with JAK3 mutations in T-ALL, and HOXA9 cooperates with activated STAT5 to transform hematopoietic stem and progenitor cells to promote leukemogenesis.

Colorectal Tumors Require NUAK1 for Protection from Oxidative Stress 632
Précis: The AMPK family member NUAK1 drives the nuclear translocation of the master antioxidant transcription factor NRF2 to drive colorectal cancer initiation and tumorigenesis.

Allele-Specific Mechanisms of Activation of MEK1 Mutants Determine Their Properties 648
Précis: Characterization of 17 tumor-associated MEK1 mutations reveals distinct mechanisms of ERK activation and suggests ATP-competitive inhibitors may inhibit allosteric inhibitor-insensitive mutants.

See commentary, p. 534

Combination therapies targeting MEK and CDK4/6 are under investigation for the treatment of patients with melanoma, but optimal dosing schedules and potential mechanisms of resistance have not been determined. Teh and colleagues found that continuous MEK inhibition (MEKi) with intermittent CDK4/6 inhibition (CDK4/6i) resulted in maximal antitumor activity with limited toxicity. Acquired resistance to MEKi plus CDK4/6i was linked to increased S6 phosphorylation, and an mTORC inhibitor overcame resistance in vivo. Similarly, Romano and colleagues investigated mechanisms of resistance to MEKi plus CDK4i in NRAS-mutant melanoma and uncovered a rare preexisting mutation (PI3KCAE545K) that activated S6K1 to increase S6 phosphorylation and promote resistance to MEKi plus CDK4i. Collectively, these findings suggest that mTORC inhibition may overcome acquired resistance to MEKi plus CDK4i. For details, please see the articles by Teh and colleagues on page 568 and Romano and colleagues on page 556.