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Précis: Clinically available drugs that disrupt neurotransmitter-induced G protein-coupled receptor signaling inhibit growth of tumor types with neuroendocrine features.
See commentary, p. 1333

Hypoxia Induces Phenotypic Plasticity and Therapy Resistance in Melanoma via the Tyrosine Kinase Receptors ROR1 and ROR2 .................. 1378
Précis: WNT5A signaling promotes a phenotype switch to more invasive, BRAF inhibitor-resistant melanomas in response to hypoxia via reciprocal regulation of ROR1 and ROR2.
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What a Tangled Web We Weave: Emerging Resistance Mechanisms to Inhibition of the Phosphoinositide 3-Kinase Pathway ............. 1345
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Activation of the PD-1 Pathway Contributes to Immune Escape in EGFR-Driven Lung Tumors . . . . 1355
Précis: EGFR pathway activation promotes tumor immune evasion in NSCLC via induction of PD-1, PD-L1, and immunosuppressive, tumor-promoting cytokines.
See commentary, p. 1333

Q&A: Elizabeth Blackburn on Telomerase and Tumors . . . . . . . 1323
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Précis: WNT5A signaling promotes a phenotype switch to more invasive, BRAF inhibitor-resistant melanomas in response to hypoxia via reciprocal regulation of ROR1 and ROR2.
Akbay and colleagues found that EGFR activation in non–small cell lung cancer (NSCLC) resulted in an immunosuppressive microenvironment characterized by upregulation of programmed cell death 1 (PD-1) and its ligand PD-L1, reduction of CD8+ cytotoxic T cells, and induction of tumor-promoting cytokines. PD-1 blockade suppressed EGFR-driven NSCLC growth via increased T-cell infiltration and improved cytotoxic T-cell function, as well as reduced expression of immunosuppressive cytokines. PD-L1 induction in human NSCLC cells was dependent on EGFR activation, as treatment with EGFR kinase inhibitors decreased PD-L1 levels. These results define a non–cell-autonomous role of oncogenic EGFR in promoting immune evasion in lung cancer and suggest that dual inhibition of EGFR and PD-1 may be effective in EGFR-mutant NSCLC. For details, please see the article by Akbay and colleagues on page 1355.

Discovery of a Mutant-Selective Covalent Inhibitor of EGFR that Overcomes T790M-Mediated Resistance in NSCLC


Précis: CO-1686 specifically and irreversibly inhibits mutant EGFR proteins including EGFR(T790M) while sparing wild-type EGFR activity.

Acknowledgment to Reviewers

For more News and Research Watch, visit Cancer Discovery online at http://CDnews.aacrjournals.org. Online-only News stories include the following:

• Checkpoint Inhibitor Shows Promise in Smokers
• Antibody–Drug Conjugate May Inhibit Pancreatic Cancer
• T-DM1 Aids Patients with Advanced Breast Cancer
• Ramucirumab Takes Steps Forward in Gastric Cancer
• Decade-Long Survival Possible after Ipilimumab
• Nanopharmaceutical May Offer Benefits in Combinations

ON THE COVER

A Chimeric RNA Characteristic of Rhabdomyosarcoma in Normal Myogenesis Process


Précis: A PAX3–FOXO1 chimeric RNA identical to the gene fusion expressed in alveolar rhabdomyosarcoma is transiently expressed in normal cells during skeletal muscle differentiation.

Discovery of a Mutant-Selective Covalent Inhibitor of EGFR that Overcomes T790M-Mediated Resistance in NSCLC


Précis: Implementation of drug combinations predicted to be effective based on ex vivo drug sensitivity and resistance testing of acute myeloid leukemia samples led to clinical responses.

See commentary, p. 1336