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A Systems Biology Approach to Personalizing Therapeutic Combinations ................. 1339
L.N. Kwong, T.P. Heffernan, and L. Chin
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.

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Individualized Systems Medicine Strategy to Tailor Treatments for Patients with Chemorefractory Acute Myeloid Leukemia .......... 1416


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.
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A Chimeric RNA Characteristic of Rhabdomyosarcoma in Normal Myogenesis Process ................. 1394

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 ................. 1404

Précis: CO-1686 specifically and irreversibly inhibits mutant EGFR proteins including EGFR(790M) while sparing wild-type EGFR activity.

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