A Genome-Wide Scan Identifies Variants in NFIB Associated with Metastasis in Patients with Osteosarcoma ..........920

Précis: The risk variant rs7034162 in NFIB contributes to osteosarcoma metastasis susceptibility.

Real-Time Imaging Reveals Local, Transient Vascular Permeability, and Tumor Cell Intravasation Stimulated by TIE2hi Macrophage–Derived VEGFA ..........932

Précis: Hyperpermeability of tumor vasculature is dynamic and restricted to the Tumor MicroEnvironment of Metastasis (TMEM).

See commentary, p. 906

HOXB7 Is an ERα Cofactor in the Activation of HER2 and Multiple ER Target Genes Leading to Endocrine Resistance ..........944

Précis: HOXB7 is upregulated by MYC-mediated suppression of miR-196a and enhances expression of ER target genes in tamoxifen-resistant breast cancer cells.

See commentary, p. 909
Combined EGFR/MEK Inhibition Prevents the Emergence of Resistance in EGFR-Mutant Lung Cancer .......................... 960
Précis: Acquired resistance to EGFR inhibitors can be prevented with dual EGFR and MEK inhibition, which results in prolonged ERK1/2 inhibition and increased apoptosis in EGFR-mutant NSCLC.

Synthetic Lethal Approaches Exploiting DNA Damage in Aggressive Myeloma ................. 972
Précis: Upregulation of MYC in multiple myeloma cells drives DNA damage via replicative stress and ROS induction, and confers sensitivity to ATR inhibitors and small-molecule inducers of ROS.

Mass Cytometric Functional Profiling of Acute Myeloid Leukemia Defines Cell-Cycle and Immunophenotypic Properties That Correlate with Known Responses to Therapy ............... 988
G.K. Behbehani, N. Samusik, Z.B. Bjornson, W.J. Fantl, B.C. Medeiros, and G.P. Nolan
Précis: High-dimensional analysis of patient-derived AML cells using mass cytometry identifies changes in immunophenotypic patterns and cell-cycle kinetics that are predictive of AML subtype and chemotherapeutic response.
See commentary, p. 912

ON THE COVER
Tricker, Xu, and colleagues found that combined treatment with the mutant EGFR-selective inhibitor WZ4002 and the MEK inhibitor trametinib delayed the development of acquired resistance in EGFR inhibitor-naïve and EGFR^{T790M}-positive lung cancer cells. WZ4002/trametinib treatment prevented ERK1/2 reactivation and increased apoptosis. Combination treatment was also significantly more effective than WZ4002 alone in suppressing tumor regrowth in xenograft models and a genetically engineered mouse model of EGFR^{T790M}-mutant lung cancer. Although EGFR and ERK inhibition were maintained in the majority of WZ4002/trametinib-resistant tumor nodules, both AKT and S6 were frequently reactivated, and the addition of an mTOR inhibitor restored WZ4002/trametinib sensitivity in vitro and in vivo. These results highlight the potential clinical utility of initial cotargeting of EGFR and MEK to prevent the emergence of acquired resistance in EGFR-mutant lung cancer. For details, please see the article by Tricker, Xu, and colleagues on page 960.