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Molecular Heterogeneity and Receptor Coamplification Drive Resistance to Targeted Therapy in MET-Amplified Esophagogastric Cancer .................. 1271
Précis: Resistance to MET inhibition in MET-amplified esophagogastric cancer is mediated by KRAS mutation, coamplification of HER2 and/or EGFR, and intratumor heterogeneity in MET amplification.

RESEARCH ARTICLES

Convergence of Acquired Mutations and Alternative Splicing of CD19 Enables Resistance to CART-19 Immunotherapy .......... 1282
Précis: Alternative splicing of CD19 prevents its recognition by CD19-targeted chimeric antigen receptor (CAR) T cells and can underlie resistance to CD19 CAR T-cell therapy in patients with B-ALL.
See commentary, p. 1238

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A Cross-Species Analysis in Pancreatic Neuroendocrine Tumors Reveals Molecular Subtypes with Distinctive Clinical, Metastatic, Developmental, and Metabolic Characteristics ……1296


Précis: Integrated mRNA and miRNA profiling of mouse and human pancreatic neuroendocrine tumors (PanNET) identifies distinct subtypes and validates the RIP1-Tag2 mouse model as representative of human PanNET.

Dual Roles of RNF2 in Melanoma Progression ……………………1314


Précis: The prometastatic and oncogenic functions of RNF2 in melanoma are driven by differential changes in gene expression regulated by chromatin modification or recruitment of transcriptional activators, respectively. See commentary, p. 1241

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Infection Exposure Is a Causal Factor in B-cell Precursor Acute Lymphoblastic Leukemia as a Result of Pax5-Inherited Susceptibility …………………….1328


Précis: Delayed exposure to infection promotes B-cell precursor acute lymphoblastic leukemia in the context of inactivating germline Pax5 mutations, which create an aberrant progenitor cell compartment that is susceptible to Jak3 mutation-induced transformation. See commentary, p. 1244

ON THE COVER

Chimeric antigen receptor T-cell therapy targeting CD19 (CART-19) is clinically active in pediatric B-cell acute lymphoblastic leukemia (B-ALL), but loss of the CD19 epitope has been implicated in tumor relapse. Sotillo and colleagues compared paired CD19-positive, pre-CART-19 and CD19-negative, post-CART-19 relapsed pediatric B-ALL samples and found hemizygous deletion of CD19 and mutations affecting CD19 exon 2 in a subset of relapsed tumors. Alternatively spliced CD19 transcripts were also specifically identified in relapsed samples, including a splice variant with exon 2 skipping (CD19 Δex2) that resulted in expression of a functional truncated protein. CD19 Δex2 expression provided a proliferative advantage and partially rescued the effects of CD19 loss. In addition, CD19 Δex2-expressing cells remained viable upon CART-19 exposure, suggesting that alternative splicing can lead to epitope loss and evasion from CAR T-cell therapy. For details, please see the article by Sotillo and colleagues on page 1282.