In The Spotlight

Overcoming Antigen Escape with CAR T-cell Therapy 1238
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RNF2 E3 or Not to E3: Dual Roles of RNF2 Overexpression in Melanoma 1241
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Infection and the Perils of B-cell Activation 1244
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Pancreatic Cancer Metabolism: Breaking It Down to Build It Back Up 1247
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RICTOR Amplification Defines a Novel Subset of Patients with Lung Cancer Who May Benefit from Treatment with mTORC1/2 Inhibitors 1262
Précis: Amplification of RICTOR is present in 8–13% of patients with lung cancer and is associated with a greater response to mTORC1/2 inhibition.

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.

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.
For more information please visit http://www.transcriptional activators, respectively by chromatin modification or recruitment of differential changes in gene expression regulated functions of RNF2 in melanoma are driven by representative of human PanNET and validates the RIP1-Tag2 mouse model as tumors (PanNET) identifies distinct subtypes of mouse and human pancreatic neuroendocrine Neuroendocrine Tumors Reveals Molecular Subtypes with Distinctive Clinical, Metastatic, Developmental, and Metabolic Characteristics ..........1296 A. Sadanandam, S. Wulfschlegel, C.A. Lyssiotis, C. Grötzing, S. Barbi, S. Bersani, J. Körner, I. Wafy, A. Mafficini, R.T. Lawlor, M. Simbolo, J.M. Asara, H. Bläker, L.C. Cantley, B. Wiedenmann, A. Scarpa, and D. Hanahan

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.


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


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

Acknowledgment to Reviewers .............1344

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.