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### VIEWS
In The Spotlight

**Unraveling the Architecture of Classic Hodgkin Lymphoma One Cell at a Time** 342
D.A.C. Fisher and S.T. Oh
See article, p. 406

**Regulatory T Cells Keep Pancreatic Cancer at Bay** 345
B. Aykut, R. Chen, and G. Miller
See article, p. 422

**TBK1 Activation by VHL Loss in Renal Cell Carcinoma: A Novel HIF-Independent Vulnerability** 348
Z. Bakouny and D.A. Barbie
See article, p. 460

### RESEARCH BRIEFS

**Circadian Regulator CLOCK Recruits Immune-Suppressive Microglia into the GBM Tumor Microenvironment** 371

**Précis:** The circadian-rhythm protein CLOCK was implicated in increasing stem-like properties of glioblastoma cells and promoting infiltration of immunosuppressive microglia in the tumor microenvironment.

**Type I Interferon Regulates a Coordinated Gene Network to Enhance Cytotoxic T Cell–Mediated Tumor Killing** 382

**Précis:** UBA7, encoded by an interferon-stimulated gene (ISG), suppressed tumor growth in mouse models of breast cancer via covalently conjugating the protein ISG15 to other ISG products, including STAT1/2, to mediate an antitumor immune response.

### RESEARCH ARTICLES

**Acalabrutinib plus Obinutuzumab in Treatment-Naïve and Relapsed/Refractory Chronic Lymphocytic Leukemia** 394

**Précis:** In a phase Ib/II clinical trial, the combination of obinutuzumab with the BTK inhibitor acalabrutinib was effective and tolerable in patients with treatment-naïve and relapsed/refractory chronic lymphocytic leukemia.

**Single-Cell Transcriptome Analysis Reveals Disease-Defining T-cell Subsets in the Tumor Microenvironment of Classic Hodgkin Lymphoma** 406

Précis: Single-cell RNA sequencing, immunohistochemistry, and imaging mass cytometry identified immunosuppressive LAG3+ T cells near malignant cells in the MHC class II− classic Hodgkin lymphoma microenvironment.

See commentary, p. 342

Regulatory T-cell Depletion Alters the Tumor Microenvironment and Accelerates Pancreatic Carcinogenesis ............... 422


Précis: Contrary to prior results, Treg depletion in mouse models of pancreatic ductal adenocarcinoma sped carcinogenesis by altering the fibroblast and myeloid-cell populations in the tumor microenvironment.

See commentary, p. 345

Selective Inhibition of HDAC3 Targets Synthetic Vulnerabilities and Activates Immune Surveillance in Lymphoma... 440


Précis: The epigenetic and transcriptional effects of CREBBP hotspot mutations in diffuse large B-cell lymphoma (DLBCL) were reversed by HDAC3 inhibition, which synergized with PD-L1 blockade in a mouse model of DLBCL.

TBK1 Is a Synthetic Lethal Target in Cancer with VHL Loss ............... 460


Précis: TANK-binding kinase 1 is hyperactivated in VHL-mutant clear-cell renal cell carcinoma, and the protein’s role in this malignancy appears to be distinct from its established function in innate immunity.

See commentary, p. 348

Correction

Correction: Oral Mucosal Organoids as a Potential Platform for Personalized Cancer Therapy ............... 476

ON THE COVER Cancer-cell stemness is associated with immunosuppression and poor prognosis in glioblastoma and many other malignancies. Chen and colleagues found that depletion of the circadian-rhythm gene CLOCK in glioma stem cells (GSC) led to reduced self-renewal capabilities and decreased markers of immunosuppressive microglia infiltration. Mechanistically, CLOCK-depleted cells had reduced levels of OLFML3, encoding a secreted protein involved in intercellular interactions. In mouse models, tumors derived from CLOCK-depleted GSCs were less aggressive than those derived from control GSCs, leading to increased survival in mice bearing CLOCK-depleted tumors, and exhibited reduced signs of stemness and microglia infiltration. Bolstering the proposed mechanism, tumors derived from OLFML3-depleted GSCs were also less aggressive than controls. For details, please see the article by Chen and colleagues on page 371.
CANCER DISCOVERY

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