

# CANCER DISCOVERY CONTENTS

MARCH 2020 ■ VOLUME 10 ■ NUMBER 3

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## VIEWS In The Spotlight

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J. Chou, D.A. Quigley, T.M. Robinson, F.Y. Feng, and A. Ashworth

## RESEARCH BRIEFS

**Circadian Regulator CLOCK Recruits Immune-Suppressive Microglia into the GBM Tumor Microenvironment** ..... 371  
P. Chen, W.-H. Hsu, A. Chang, Z. Tan, Z. Lan, A. Zhou, D.J. Spring, F.F. Lang, Y.A. Wang, and R.A. DePinho

**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  
J.-B. Fan, S. Miyauchi, H.-Z. Xu, D. Liu, L.J.Y. Kim, C. Burkart, H. Cheng, K.-i. Arimoto, M. Yan, Y. Zhou, B. Györfy, K.-P. Knobloch, J.N. Rich, H. Cang, X.-D. Fu, and D.-E. Zhang

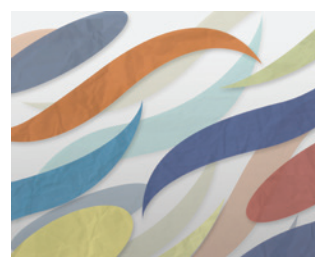
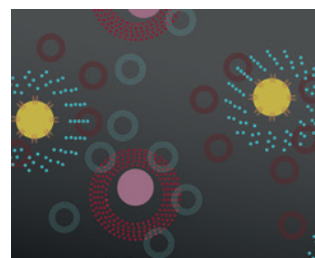
**Précis:** UBA7, encoded by an interferon-stimulated gene (ISG), suppressed tumor growth in mouse models of breast cancer via covalently conjugating the protein ISG15 to other ISG products, including STAT1/2, to mediate an antitumor immune response.

## RESEARCH ARTICLES

**Acalabrutinib plus Obinutuzumab in Treatment-Naïve and Relapsed/Refractory Chronic Lymphocytic Leukemia** ..... 394  
J.A. Woyach, J.S. Blachly, K.A. Rogers, S.A. Bhat, M. Jianfar, G. Lozanski, D.M. Weiss, B.L. Andersen, M. Gulrajani, M.M. Frigault, A. Hamdy, R. Izumi, V. Munugalavada, C. Quah, M.-H. Wang, and J.C. Byrd

**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  
T. Aoki, L.C. Chong, K. Takata, K. Milne, M. Hav, A. Colombo, E.A. Chavez, M. Nissen, X. Wang, T. Miyata-Takata, V. Lam, E. Viganò, B.W. Woolcock, A. Telenius, M.Y. Li, S. Healy, C. Ghesquiere, D. Kos, T. Goodyear, J. Veldman, A.W. Zhang, J. Kim, S. Saberi, J. Ding,





P. Farinha, A.P. Weng, K.J. Savage, D.W. Scott, G. Krystal, B.H. Nelson, A. Mottok, A. Merchant, S.P. Shah, and C. Steidl

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

See commentary, p. 342

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



Y. Zhang, J. Lazarus, N.G. Steele, W. Yan, H.-J. Lee, Z.C. Nwosu, C.J. Halbrook, R.E. Menjivar, S.B. Kemp, V.R. Siriwhorachai, A. Velez-Delgado, K. Donahue, E.S. Carpenter, K.L. Brown, V. Irizarry-Negron, A.C. Nevison, A. Vinta, M.A. Anderson, H.C. Crawford, C.A. Lyssiotis, T.L. Frankel, F. Bednar, and M. Pasca di Magliano

**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



P. Mondello, S. Tadros, M. Teater, L. Fontan, A.Y. Chang, N. Jain, H. Yang, S. Singh, H.-Y. Ying, C.-S. Chu, M.C.J. Ma, E. Toska, S. Alig, M. Durant,



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E. de Stanchina, S. Ghosh, A. Mottok, L. Nastoupil, S.S. Neelapu, O. Weigert, G. Inghirami, J. Baselga, A. Younes, C. Yee, A. Dogan, D.A. Scheinberg, R.G. Roeder, A.M. Melnick, and M.R. Green

**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

L. Hu, H. Xie, X. Liu, F. Potjewy, L.I. James, E.M. Wilkerson, L.E. Herring, L. Xie, X. Chen, J.C. Cabrera, K. Hong, C. Liao, X. Tan, A.S. Baldwin, K. Gong, and Q. Zhang

**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.

