

# CANCER DISCOVERY CONTENTS

DECEMBER 2020 ■ VOLUME 10 ■ NUMBER 12

**IN THIS ISSUE** Highlighted research articles ..... 1775

**NEWS IN BRIEF** Important news stories affecting the community ..... 1780

**RESEARCH WATCH** Selected highlights of recent articles of exceptional significance from the cancer literature ..... 1784

**ONLINE** For more News and Research Watch, visit *Cancer Discovery* online at <http://cancerdiscovery.aacrjournals.org/CDNews>.

## VIEWPOINTS In The Spotlight

**A Sweet Approach to Heat Up Cancer Response to Immunotherapy** ..... 1789

O.M.T. Pearce and H. Läubli

See article, p. 1872

**BETs Need Greens: Folate Deficiency and Resistance to MYC-Targeted Therapies** ... 1791

L. Marando and B.J.P. Huntly

See article, p. 1894

**Histone H3 G34 Tail Mutations in Cancer: Actions in *Cis* and *Trans* to Alter Chromatin and Gene Expression** ..... 1794

J.D. Licht

See article, p. 1968

**REVIEWS Targeting Metabolic Plasticity and Flexibility Dynamics for Cancer Therapy** ..... 1797

S.-M. Fendt, C. Frezza, and A. Erez

**Tumor Mutational Burden as a Predictive Biomarker in Solid Tumors** ..... 1808

D. Sha, Z. Jin, J. Budczies, K. Kluck, A. Stenzinger, and F.A. Sinicrope

**RESEARCH BRIEF KEAP1/NFE2L2 Mutations Predict Lung Cancer Radiation Resistance That Can Be Targeted by Glutaminase Inhibition** .... 1826

M.S. Binkley, Y.-J. Jeon, M. Nesselbush, E.J. Moding, B.Y. Nabat, D. Almanza, C. Kunder, H. Stehr, C.H. Yoo, S. Rhee, M. Xiang, J.J. Chabon, E. Hamilton, D.M. Kurtz, L. Gojenola, S.G. Owen, R.B. Ko, J.H. Shin, P.G. Maxim, N.S. Lui, L.M. Backhus, M.F. Berry, J.B. Shrager, K.J. Ramchandran, S.K. Padda, M. Das, J.W. Neal, H.A. Wakelee, A.A. Alizadeh, B.W. Loo Jr, and M. Diehn

**Précis:** In patients with non-small cell lung cancer, local recurrence following radiotherapy was predicted by loss-of-function *KEAP1* mutations or gain-of-function *NFE2L2* mutations, and this resistance could be overcome by glutaminase inhibition.

**RESEARCH ARTICLES Prognostic and Predictive Impact of Circulating Tumor DNA in Patients with Advanced Cancers Treated with Immune Checkpoint Blockade** ..... 1842

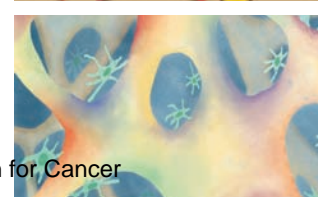
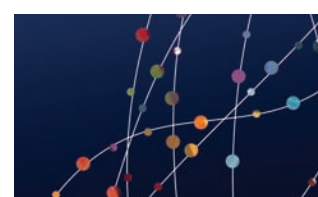
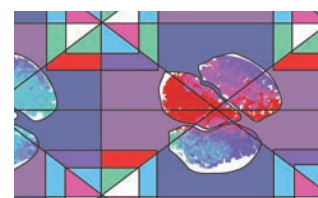


Q. Zhang, J. Luo, S. Wu, H. Si, C. Gao, W. Xu, S.E. Abdullah, B.W. Higgs, P.A. Dennis, M.S. van der Heijden, N.H. Segal, J.E. Chaff, T. Hembrough, J.C. Barrett, and M.D. Hellmann

**Précis:** Patients receiving immune checkpoint blockade therapies who had lower circulating tumor DNA (ctDNA) variant allele frequencies on treatment compared with pretreatment had a higher objective response rate and improved overall survival, suggesting that ctDNA analysis may complement existing prognostic techniques.

**Multidimensional Analyses of Donor Memory-Like NK Cells Reveal New Associations with Response after Adoptive Immunotherapy for Leukemia** ..... 1854

M.M. Berrien-Elliott, A.F. Cashen, C.C. Cubitt, C.C. Neal, P. Wong, J.A. Wagner, M. Foster, T. Schappe, S. Desai, E. McClain, M. Becker-Hapak, J.A. Foltz, M.L. Cooper, N. Jaeger, S.N. Srivatsan, F. Gao, R. Romee, C.N. Abboud, G.L. Uy, P. Westervelt, M.A. Jacoby, I. Pusic, K.E. Stockerl-Goldstein, M.A. Schroeder, J. DiPersio, and T.A. Fehniger





**Précis:** In patients with acute myeloid leukemia receiving memory-like natural killer (NK)-cell therapy, expression of the inhibitory immune checkpoint receptor NKG2A by the memory-like NK cells was associated with lack of treatment response.

**Pharmacologic Suppression of B7-H4 Glycosylation Restores Antitumor Immunity in Immune-Cold Breast Cancers** ..... 1872

X. Song, Z. Zhou, H. Li, Y. Xue, X. Lu, I. Bahar, O. Kepp, M.-C. Hung, G. Kroemer, and Y. Wan

**Précis:** Preventing glycosylation of the immunosuppressive transmembrane protein B7-H4 increased its ubiquitination and subsequent degradation, and inhibition of B7-H4 glycosylation *in vivo* improved immunogenicity of immune-cold tumors.

See commentary, p. 1789

**The Folate Cycle Enzyme MTHFR Is a Critical Regulator of Cell Response to MYC-Targeting Therapies** ..... 1894

A. Su, F. Ling, C. Vaganay, G. Sodaro, C. Benaksas, R. Dal Bello, A. Forget, B. Pardieu, K.H. Lin, J.C. Rutter, C.F. Bassil, G. Fortin, J. Pasanisi, I. Antony-Debré, G. Alexe, J.-F. Benoist, A. Pruvost, Y. Pikman, J. Qi, M.-H. Schlageter, J.-B. Micol, G. Roti, T. Cluzeau, H. Dombret, C. Preudhomme, N. Fenouille, L. Benajiba, H.M. Golan, K. Stegmaier, C. Lobry, K.C. Wood, R. Itzykson, and A. Puissant

**Précis:** *In vitro* and *in vivo* experiments using models of acute myeloid leukemia showed that the folate cycle enzyme MTHFR mediated response to BET inhibitors, which target oncogenic MYC expression and are in phase I and II clinical trials.

See commentary, p. 1791

**CRISPR-GEMM Pooled Mutagenic Screening Identifies KMT2D as a Major Modulator of Immune Checkpoint Blockade** ..... 1912

G. Wang, R.D. Chow, L. Zhu, Z. Bai, L. Ye, F. Zhang, P.A. Renauer, M.B. Dong, X. Dai, X. Zhang, Y. Du, Y. Cheng, L. Niu, Z. Chu, K. Kim, C. Liao, P. Clark, Y. Errami, and S. Chen

**Précis:** In genetically engineered mouse models, loss-of-function mutations in *Kmt2d*, which encodes a histone methyltransferase often mutated in human cancers, led to increased anti-PD-1 efficacy against a variety of cancer types.

 AC icon indicates AuthorChoice

For more information please visit <http://www.aacrjournals.org>

**Somatic Mutations Drive Specific, but Reversible, Epigenetic Heterogeneity States in AML** ..... 1934

S. Li, X. Chen, J. Wang, C. Meydan, J.L. Glass, A.H. Shih, R. Delwel, R.L. Levine, C.E. Mason, and A.M. Melnick

**Précis:** Mutations that drive acute myeloid leukemia, especially in combination, induced epigenetic alterations prior to leukemogenesis, resulting in epigenetic diversity that was associated with poor prognosis in patients.

**Combined Proteomic and Genetic Interaction Mapping Reveals New RAS Effector Pathways and Susceptibilities** ..... 1950

M.R. Kelly, K. Kostyrko, K. Han, N.A. Mooney, E.E. Jeng, K. Spees, P.T. Dinh, K.L. Abbott, D.M. Gwinn, E.A. Sweet-Cordero, M.C. Bassik, and P.K. Jackson

**Précis:** A new method coupled identification of protein-protein interactions and synthetic-lethal relationships to reveal previously unknown and functionally relevant RAS pathway interactors in mutant *KRAS*-driven lung adenocarcinoma models.

**H3.3 G34W Promotes Growth and Impedes Differentiation of Osteoblast-Like Mesenchymal Progenitors in Giant Cell Tumor of Bone** ..... 1968



S. Khazaei, N. De Jay, S. Deshmukh, L.D. Hendrikse, W. Jawhar, C.C.L. Chen, L.G. Mikael, D. Faury, D.M. Marchione, J. Lanoix, É. Bonnell, T. Ishii, S.U. Jain, K. Rossokhata, T.S. Sihota, R. Eveleigh, V. Lisi, A.S. Harutyunyan, S. Jung, J. Karamchandani, B.C. Dickson, R. Turcotte, J.S. Wunder, P. Thibault, P.W. Lewis, B.A. Garcia, S.C. Mack, M.D. Taylor, L. Garzia, C.L. Kleinman, and N. Jabado

**Précis:** G34W mutation in histone 3.3, found in most cases of giant cell tumor of bone, caused large-scale epigenetic remodeling that led to aberrant differentiation and recruitment of the giant osteoclasts that underlie the pathologic features of this tumor type.

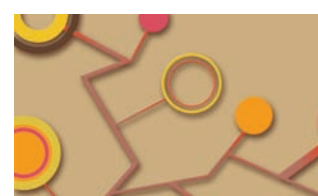
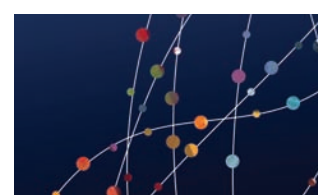
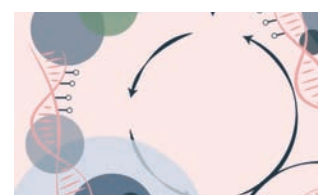
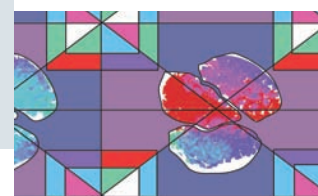
See commentary, p. 1794

**Correction**

**Correction: The Pancreatic Cancer Microbiome Promotes Oncogenesis by Induction of Innate and Adaptive Immune Suppression** ..... 1988

# CANCER DISCOVERY CONTENTS

**ON THE COVER** Activation of the KEAP1-NFE2L2 stress-response pathway has been implicated as a potential cause of resistance to radiotherapy in non-small cell lung cancer (NSCLC). In a study of 232 patients with NSCLC undergoing radiotherapy or surgery with curative intent, Binkley, Jeon, and colleagues found that loss-of-function mutations in *KEAP1* or gain-of-function mutations in *NFE2L2* were associated with increased risk of local recurrence after treatment. *In vitro*, treatment with a glutaminase inhibitor increased the susceptibility of radiation-resistant *KEAP1*- and *NFE2L2*-mutant lung cancer cells to radiation, consistent with recent work showing that glutamine metabolism is a dependency in *KEAP1*-deficient cells. For more information, see the article by Binkley, Jeon, and colleagues on page 1826.



# CANCER DISCOVERY

## 10 (12)

*Cancer Discov* 2020;10:OF4-1988.

**Updated version** Access the most recent version of this article at:  
<http://cancerdiscovery.aacrjournals.org/content/10/12>

**E-mail alerts** [Sign up to receive free email-alerts](#) related to this article or journal.

**Reprints and Subscriptions** To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at [pubs@aacr.org](mailto:pubs@aacr.org).

**Permissions** To request permission to re-use all or part of this article, use this link <http://cancerdiscovery.aacrjournals.org/content/10/12>. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.