

CANCER DISCOVERY CONTENTS

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

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RESEARCH ARTICLES

Oral Mucosal Organoids as a Potential Platform for Personalized Cancer Therapy 852

E. Driehuis, S. Kolders, S. Spelier, K. Löhmußaar, S.M. Willems, L.A. Devriese, R. de Bree, E.J. de Ruiter, J. Korving, H. Begthel, J.H. van Es, V. Geurts, G.-W. He, R.H. van Jaarsveld, R. Oka, M.J. Muraro, J. Vивиé, M.M.J.M. Zandvliet, A.P.A. Hendrickx, N. Iakobachvili, P. Sridevi, O. Kranenburg, R. van Boxtel, G.J.P.L. Kops, D.A. Tuveson, P.J. Peters, A. van Oudenaarden, and H. Clevers

Précis: Organoids derived from head and neck squamous cell carcinoma (HNSCC) and matching normal tissue allow for the *in vitro* characterization of the genetics, histology, and drug sensitivity of HNSCC.

See commentary, p. 828

Rational Targeting of Cooperating Layers of the Epigenome Yields Enhanced Therapeutic Efficacy against AML 872

C. Duy, M. Teater, F.E. Garrett-Bakelman, T.C. Lee, C. Meydan, J.L. Glass, M. Li, J.C. Hellmuth, H.P. Mohammad, K.N. Smitheman, A.H. Shih, O. Abdel-Wahab, M.S. Tallman, M.L. Guzman, D. Muench, H.L. Grimes, G.J. Roboz, R.G. Kruger, C.L. Creasy, E.M. Paietta, R.L. Levine, M. Carroll, and A.M. Melnick

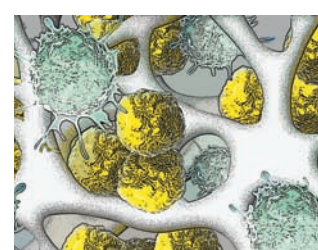
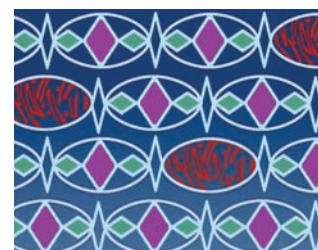
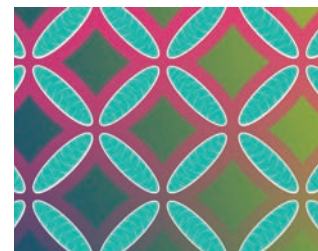
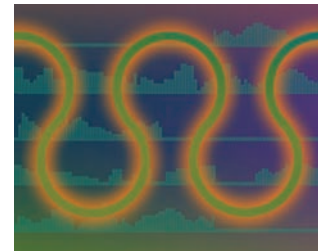
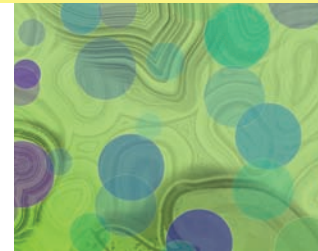
Précis: Analysis of a long-term primary acute myeloid leukemia (AML) *ex vivo* culture platform shows that combined targeting of enhancers with an LSD1 inhibitor and promoters with 5-azacytidine shows greater efficacy than monotherapy, particularly in *TET2*-mutant AML.

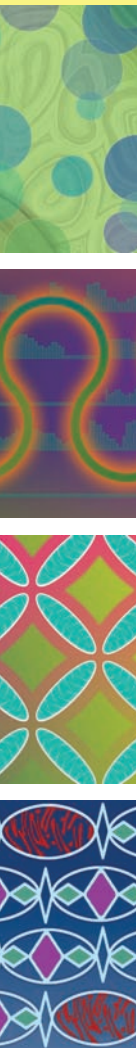
Targeting Mitochondrial Structure Sensitizes Acute Myeloid Leukemia to Venetoclax Treatment 890

X. Chen, C. Glytsou, H. Zhou, S. Narang, D.E. Reyna, A. Lopez, T. Sakellaropoulos, Y. Gong, A. Kloetgen, Y.S. Yap, E. Wang, E. Gavathiotis, A. Tsirigos, R. Tibes, and I. Aifantis

Précis: Depletion of mitochondrial proteins involved in maintenance of mitochondrial function and structure including the chaperonin CLPB is synthetically lethal with venetoclax in acute myeloid leukemia cells.

See commentary, p. 831





The TP53 Apoptotic Network Is a Primary Mediator of Resistance to BCL2 Inhibition in AML Cells 910

T. Nechiporuk, S.E. Kurtz, O. Nikolova, T. Liu, C.L. Jones, A. D'Alessandro, R. Culp-Hill, A. d'Almeida, S.K. Joshi, M. Rosenberg, C.E. Tognon, A.V. Danilov, B.J. Druker, B.H. Chang, S.K. McWeeney, and J.W. Tyner

Précis: Inactivation of p53 and proapoptotic proteins promotes resistance to venetoclax in acute myeloid leukemia by inducing changes in mitochondrial homeostasis and cellular metabolism.

See commentary, p. 831

Single and Dual Targeting of Mutant EGFR with an Allosteric Inhibitor 926

C. To, J. Jang, T. Chen, E. Park, M. Mushajiang, D.J.H. De Clercq, M. Xu, S. Wang, M.D. Cameron, D.E. Heppner, B.H. Shin, T.W. Gero, A. Yang, S.E. Dahlberg, K.-K. Wong, M.J. Eck, N.S. Gray, and P.A. Jänne

Précis: An allosteric inhibitor of mutant EGFR is effective against common resistance mutations alone or in combination with mutant-selective ATP-competitive EGFR inhibitors.

Mechanisms of Lymphoma Clearance Induced by High-Dose Alkylating Agents 944

C. Lossos, Y. Liu, K.E. Kolb, A.L. Christie, A. Van Scoyk, S.M. Prakadan, K. Shigemori, K.E. Stevenson, S. Morrow, O.D. Plana, C. Fraser, K.L. Jones, H. Liu, C.P. Pallasch,

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R. Modiste, Q.-D. Nguyen, J.W. Craig, E.A. Morgan, F. Vega, J.C. Aster, K.A. Sarosiek, A.K. Shalek, M.T. Hemann, and D.M. Weinstock

Précis: Analysis of *in vivo* models of double-hit lymphoma reveals the molecular mechanism underlying the role of cyclophosphamide and other alkylating agents on tumor clearance and antibody resistance.

See commentary, p. 834

A Gain-of-Function p53-Mutant Oncogene Promotes Cell Fate Plasticity and Myeloid Leukemia through the Pluripotency Factor FOXH1 962



E. Loizou, A. Banito, G. Livshits, Y.-J. Ho, R.P. Koche, F.J. Sánchez-Rivera, A. Mayle, C.-C. Chen, S. Kinalis, F.O. Bagger, E.R. Kastenhuber, B.H. Durham, and S.W. Lowe

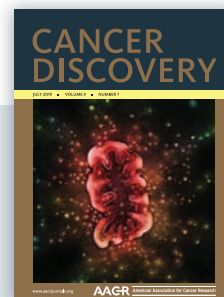
Précis: The gain-of-function mutant p53^{R172H} upregulates the transcription factor FOXH1 to promote self-renewal in acute myeloid leukemia.

Corrections

Correction: AMG 176, a Selective MCL1 Inhibitor, Is Effective in Hematologic Cancer Models Alone and in Combination with Established Therapies 980

Correction: ER Translocation of the MAPK Pathway Drives Therapy Resistance in BRAF-Mutant Melanoma 981

ON THE COVER: Chen, Glytsou, and colleagues performed a genome-wide CRISPR/Cas9 screen for genes whose inactivation would sensitize acute myeloid leukemia (AML) cells to venetoclax and identified regulators of mitochondrial organization and function, including the mitochondrial chaperonin CLPB. CLPB is elevated in AML and maintains mitochondrial cristae structure, whereas its loss promotes apoptosis by inducing cristae remodeling and mitochondrial stress responses. CLPB ablation synergized with venetoclax alone and in combination with azacitidine to inhibit AML growth. In a complementary study, Nechiporuk and colleagues performed a genome-wide CRISPR/Cas9 screen for genes whose inactivation confers venetoclax resistance in AML cells and identified members of the TP53–BAX apoptotic network. p53 and BAX expression were inversely correlated with venetoclax sensitivity in primary AML samples, and loss of p53 and BAX were associated with perturbed mitochondrial homeostasis and inhibition of a general mitochondrial stress response. Venetoclax-resistant TP53-mutant AML cells acquired a dependency on NTRK signaling for survival and were sensitive to TRK inhibitors. Together, these studies provide insights into biological mechanisms underlying responses to venetoclax in AML and suggest potential strategies to overcome venetoclax resistance. For details, please see the article by Chen, Glytsou, and colleagues on page 890 and the article by Nechiporuk and colleagues on page 910. Cover art by Yi Hu.



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