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**Highlighted research articles**

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

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

- Targeting Mitochondrial Structure Sensitizes Acute Myeloid Leukemia to Venetoclax Treatment

**Important news stories affecting the community**

- Understanding Hyperprogression in Cancer
- Microbiota Manipulated to Enhance Immunity

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- Selected highlights of recent articles of exceptional significance from the cancer literature

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

### News in Brief

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**Research Articles**

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

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

- Targeting Mitochondrial Structure Sensitizes Acute Myeloid Leukemia to Venetoclax Treatment

### Views

**In The Spotlight**

- Predictive Potential of Head and Neck Squamous Cell Carcinoma Organoids
  - S.J. Hill and A.D. D’Andrea
  - See article, p. 852

- Mitochondrial Homeostasis in AML and Gasping for Response in Resistance to BCL2 Blockade
  - M.R. Savona and J.C. Rathmell
  - See article, p. 890

- Lymphoma Chemotherapy: Hungry Macrophages Strike the Final Blow
  - F. Duval and M. De Palma
  - See article, p. 944

**Review**

- Cellular Plasticity in Cancer
  - S. Yuan, R.J. Norgard, and B.Z. Stanger
  - See commentary, p. 831
The TP53 Apoptotic Network Is a Primary Mediator of Resistance to BCL2 Inhibition in AML Cells


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

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


Mechanisms of Lymphoma Clearance Induced by High-Dose Alkylating Agents


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.

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

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

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.