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

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### Views

**In The Spotlight**

A Road Map for Precision Cancer Medicine Using Personalized Models

G. Picco and M.J. Garnett

See article, p. 462

Optimizing Next-Generation AML Therapy: Activity of Mutant IDH2 Inhibitor AG-221 in Preclinical Models

D. Thomas and R. Majeti

See article, p. 478

See article, p. 494

### Research Articles

**Personalized In Vitro and In Vivo Cancer Models to Guide Precision Medicine**


**Précis**: A precision medicine approach with high-throughput drug screening in patient-derived tumor organoids and PDX models may identify effective therapeutic strategies in patients without actionable mutations.

See commentary, p. 456

**AG-221, a First-in-Class Therapy Targeting Acute Myeloid Leukemia Harboring Oncogenic IDH2 Mutations**


**Précis**: Targeted inhibition of IDH2R140Q with the allosteric inhibitor AG-221 reduces production of the oncometabolite 2HG, promotes differentiation of malignant AML blasts, and extends survival in AML xenografts.

See commentary, p. 459

See article, p. 478

**Combination Targeted Therapy to Disrupt Aberrant Oncogenic Signaling and Reverse Epigenetic Dysfunction in IDH2- and TET2-Mutant Acute Myeloid Leukemia**


**Précis**: Mutations in TET2 or IDH2 sensitize AML cells to the DNA hypomethylating agents 5-Aza and AG-221, which induce differentiation, reverse aberrant hypermethylation, and cooperate with FLT3 inhibition to suppress AML.

See commentary, p. 459

See article, p. 494
BCL6 Antagonizes NOTCH2 to Maintain Survival of Human Follicular Lymphoma Cells ........................................ 506


Précis: BCL6 binds to and represses NOTCH2 and other NOTCH pathway genes in follicular lymphoma and GC B cells to promote their survival, and BCL6 inhibition suppresses the growth of follicular lymphoma xenografts.

Gut Microbiota Promotes Obesity-Associated Liver Cancer through PGE2-Mediated Suppression of Antitumor Immunity .................. 522


Précis: The obesity-associated gut microbial component and metabolite, LTA and DCA, promote COX2-mediated PGE2 production in senescent HSCs to suppress the antitumor immunity in mice fed a high-fat diet and promote HCC.

ON THE COVER

The activating IDH2R140Q mutation promotes accumulation of the oncometabolite (R)-2-hydroxyglutarate (2HG) to drive acute myeloid leukemia (AML) in a subset of patients. Yan and colleagues generated a potent allosteric inhibitor of IDH2R140Q, AG-221, which reduced 2HG production, promoted differentiation of AML blasts, and extended survival in AML xenografts. In a related study, Shih, Meydan, and colleagues showed that AG-221 reversed aberrant DNA hypermethylation and induced differentiation in IDH2R140Q AML cells, and the DNA hypomethylating agent 5-Azacytidine had similar effects in TET2-mutant AML. Both AG-221 and 5-Azacytidine cooperated with a FLT3 inhibitor to reverse aberrant hypermethylation and suppress leukemic stem cells. Together, these studies indicate that DNA hypomethylating agents can promote AML differentiation and may cooperate with other inhibitors. For details, please see the article by Yan and colleagues on page 478 and the article by Shih, Meydan, and colleagues on page 494.