

CANCER DISCOVERY CONTENTS

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Optimizing Next-Generation AML Therapy: Activity of Mutant IDH2 Inhibitor AG-221 in Preclinical Models 459

D. Thomas and R. Majeti

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RESEARCH ARTICLES Personalized *In Vitro* and *In Vivo* Cancer Models to Guide Precision Medicine 462



C. Pauli, B.D. Hopkins, D. Prandi, R. Shaw, T. Fedrizzi, A. Sboner, V. Sailer, M. Augello, L. Puca, R. Rosati, T.J. McNary, Y. Churakova, C. Cheung, J. Triscott, D. Pisapia, R. Rao, J.M. Mosquera, B. Robinson, B.M. Faltas, B.E. Emerling, V.K. Gadi, B. Bernard, O. Elemento, H. Beltran, F. Demichelis, C.J. Kemp, C. Grandori, L.C. Cantley, and M.A. Rubin

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.

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AG-221, a First-in-Class Therapy Targeting Acute Myeloid Leukemia Harboring Oncogenic IDH2 Mutations 478



K. Yen, J. Travins, F. Wang, M.D. David, E. Artin, K. Straley, A. Padyana, S. Gross, B. DeLaBarre, E. Tobin, Y. Chen, R. Nagaraja, S. Choe, L. Jin, Z. Konteatis, G. Cianchetta, J.O. Saunders, F.G. Salituro, C. Quivoron, P. Opolon, O. Bawa, V. Saada, A. Paci, S. Broutin, O.A. Bernard, S. de Botton, B.S. Marteyn, M. Pilichowska, Y.X. Xu, C. Fang, F. Jiang, W. Wei, S. Jin, L. Silverman, W. Liu, H. Yang, L. Dang, M. Dorsch, V. Penard-Lacronique, S.A. Biller, and S.-S.M. Su

Précis: Targeted inhibition of IDH2^{R140Q} 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

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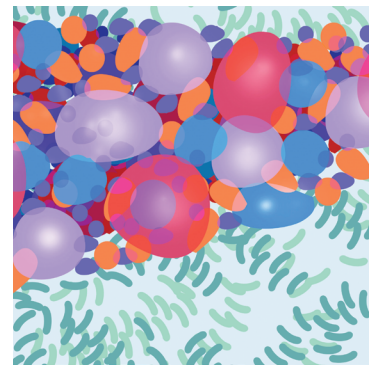
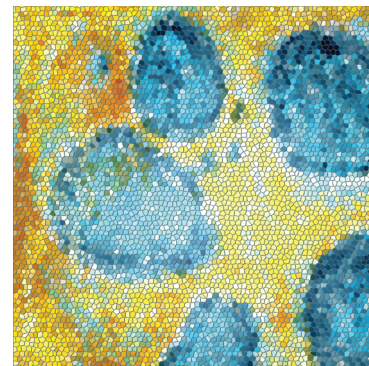
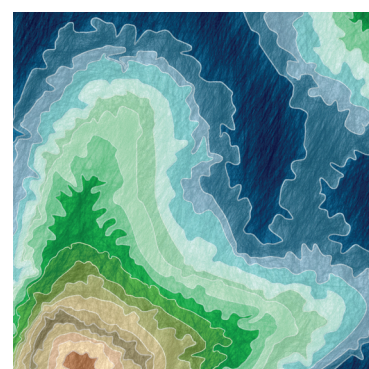
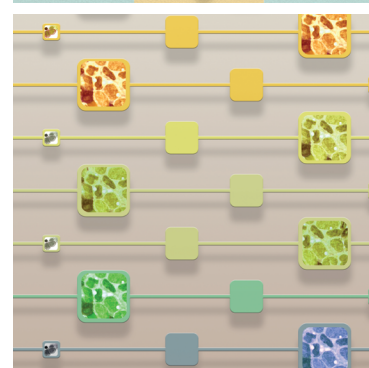
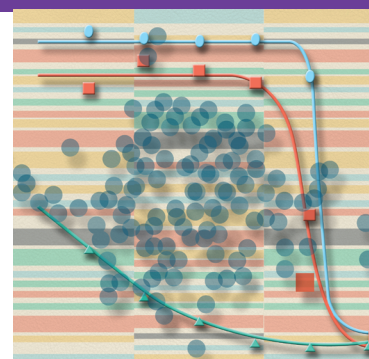
Combination Targeted Therapy to Disrupt Aberrant Oncogenic Signaling and Reverse Epigenetic Dysfunction in IDH2- and TET2-Mutant Acute Myeloid Leukemia 494

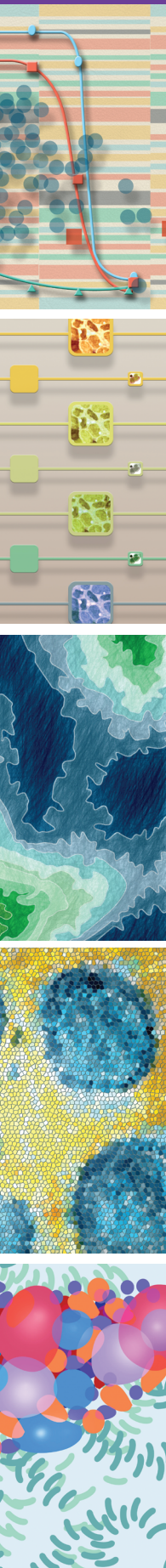
A.H. Shih, C. Meydan, K. Shank, F.E. Garrett-Bakelman, P.S. Ward, A.M. Intlekofer, A. Nazir, E.M. Stein, K. Knapp, J. Glass, J. Travins, K. Straley, C. Gliser, C.E. Mason, K. Yen, C.B. Thompson, A. Melnick, and R.L. Levine

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.

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BCL6 Antagonizes NOTCH2 to Maintain Survival of Human Follicular Lymphoma Cells 506



E. Valls, C. Lobry, H. Geng, L. Wang, M. Cardenas, M. Rivas, L. Cerchiatti, P. Oh, S.N. Yang, E. Oswald, C.W. Graham, Y. Jiang, K. Hatzi, X. Agirre, E. Perkey, Z. Li, W. Tam, K. Bhatt, J.P. Leonard, P.A. Zweidler-McKay, I. Maillard, O. Elemento, W. Ci, I. Aifantis, and A. Melnick

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.



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

T.M. Loo, F. Kamachi, Y. Watanabe, S. Yoshimoto, H. Kanda, Y. Arai, Y. Nakajima-Takagi, A. Iwama, T. Koga, Y. Sugimoto, T. Ozawa, M. Nakamura, M. Kumagai, K. Watashi, M.M. Taketo, T. Aoki, S. Narumiya, M. Oshima, M. Arita, E. Hara, and N. Ohtani

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 *IDH2*^{R140Q} mutation promotes accumulation of the oncometabolite (R)-2-hydroxyglutarate (2HG) to drive acute myeloid leukemia (AML) in a subset of patients. Yen and colleagues generated a potent allosteric inhibitor of *IDH2*^{R140Q}, 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 *IDH2*^{R140Q} 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 Yen and colleagues on page 478 and the article by Shih, Meydan, and colleagues on page 494.

