

CANCER DISCOVERY CONTENTS

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VIEWS In The Spotlight

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A. Snyder and J.D. Wolchok

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***TERT* Promoter Mutations Enhance Telomerase Activation by Long-Range Chromatin Interactions** 1212

J. Min and J.W. Shay

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S. Zhou, A.E. Treloar, and M. Lupien

RESEARCH BRIEFS Immunogenomics of Hypermutated Glioblastoma: A Patient with Germline *POLE* Deficiency Treated with Checkpoint Blockade Immunotherapy 1230

T.M. Johanss, C.A. Miller, I.G. Dorward, C. Tsien, E. Chang, A. Perry, R. Uppaluri, C. Ferguson, R.E. Schmidt, S. Dahiya, G. Ansstas, E.R. Mardis, and G.P. Dunn

Precis: Immune checkpoint blockade induced an immunologic and clinical response in a patient with germline *POLE* deficiency and a hypermutated glioblastoma.

See commentary, p. 1210

Chronic Myelogenous Leukemia-Initiating Cells Require Polycomb Group Protein EZH2 1237



H. Xie, C. Peng, J. Huang, B.E. Li, W. Kim, E.C. Smith, Y. Fujiwara, J. Qi, G. Cheloni, P.P. Das, M. Nguyen, S. Li, J.E. Bradner, and S.H. Orkin

Precis: CML leukemic stem cells are dependent on EZH2 expression and can be targeted by EZH2 inhibition to potentially eradicate leukemic stem cells in patients with CML.

See related article, p. 1248

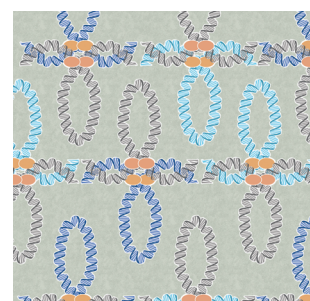
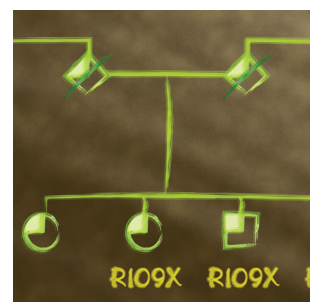
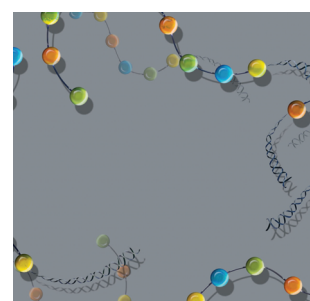
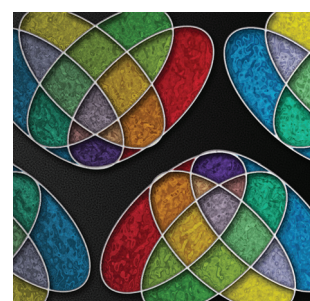
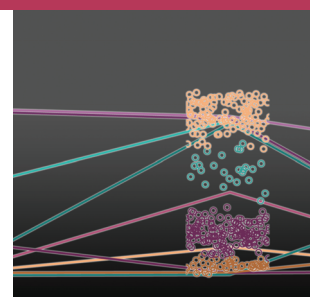
Epigenetic Reprogramming Sensitizes CML Stem Cells to Combined EZH2 and Tyrosine Kinase Inhibition 1248



M.T. Scott, K. Korfi, P. Saffrey, L.E.M. Hopcroft, R. Kinstrie, F. Pellicano, C. Guenther, P. Gallipoli, M. Cruz, K. Dunn, H.G. Jorgensen, J.E. Cassels, A. Hamilton, A. Crossan, A. Sinclair, T.L. Holyoake, and D. Vetrie

Precis: EZH2 inhibition sensitizes CML stem cells to tyrosine kinase inhibition *in vitro* and *in vivo* via reduced H3K27me3 and altered EZH2 target gene expression, which results in enhanced apoptosis.

See related article, p. 1237




Biallelic Alteration and Dysregulation of the Hippo Pathway in Mucinous Tubular and Spindle Cell Carcinoma of the Kidney 1258

R. Mehra, P. Vats, M. Cieslik, X. Cao, F. Su, S. Shukla, A.M. Udager, R. Wang, J. Pan, K. Kasaian, R. Lonigro, J. Siddiqui, K. Premkumar, G. Palapattu, A. Weizer, K.S. Hafez, J.S. Wolf Jr, A.R. Sangoi, K. Trpkov, A.O. Osunkoya, M. Zhou, G.A. Giannico, J.K. McKenney, S.M. Dhanasekaran, and A.M. Chinnaiyan

Precis: In-depth genetic characterization identifies Hippo pathway activation in mucinous tubular and spindle cell carcinoma of the kidney.

A Recurrent *ERCC3* Truncating Mutation Confers Moderate Risk for Breast Cancer 1267


 J. Vijai, S. Topka, D. Villano, V. Ravichandran, K.N. Maxwell, A. Maria, T. Thomas, P. Gaddam, A. Lincoln, S. Kazzaz, B. Wenz, S. Carmi, K.A. Schrader, S.N. Hart, S.M. Lipkin, S.L. Neuhausen, M.F. Walsh, L. Zhang, F. Lejbkiewicz, H. Rennert, Z.K. Stadler, M. Robson, J.N. Weitzel, S. Domchek, M.J. Daly, F.J. Couch, K.L. Nathanson, L. Norton, G. Rennert, and K. Offit

Precis: A protein-truncating mutation in the nucleotide excision repair gene *ERCC3* results in hypomorphic DNA repair function and is associated with increased breast cancer risk in individuals of Ashkenazi Jewish ancestry.

 AC icon indicates Author Choice

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

RESEARCH ARTICLE **Long-Range Chromatin Interactions Drive Mutant *TERT* Promoter Activation** 1276

 S.C. Akıncılar, E. Khattar, P.L.S. Boon, B. Unal, M.J. Fullwood, and V. Tergaonkar

Precis: Cancer-specific mutations in the *TERT* promoter that permit binding of GABPA facilitate long-range chromatin interactions and *TERT* expression.

See commentary, p. 1212

ON THE COVER

Tyrosine kinase inhibitors (TKI) successfully target BCR-ABL1 in chronic myelogenous leukemia (CML), but the cure rate is low due in part to the resistance of leukemic stem cells (LSC) to TKIs. In two related studies, Xie and colleagues and Scott, Korfi, and colleagues discovered a dependence of CML LSCs on EZH2 that might be targeted to eradicate LSCs. CML LSCs exhibited upregulation of EZH2 and deregulation of polycomb repressive complex 2 target genes, and suppression of EZH2 reduced colony-forming ability and induced apoptosis in LSCs alone and in combination with TKIs. *In vivo*, genetic inactivation or pharmacologic inhibition of EZH2 reduced the LSC population and prolonged survival. These studies indicate that EZH2 inhibition may eliminate CML LSCs and support further clinical investigation of EZH2 inhibitors in combination with TKIs in patients with CML. For details, please see the article by Xie and colleagues on page 1237 and the article by Scott, Korfi, and colleagues on page 1248.

