

CANCER DISCOVERY CONTENTS

JANUARY 2018 ■ VOLUME 8 ■ NUMBER 1

IN THIS ISSUE Highlighted research articles 1

NEWS IN BRIEF Important news stories affecting the community 4

RESEARCH WATCH Selected highlights of recent articles of exceptional significance from the cancer literature 9

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

VIEWES In The Spotlight

Genomic Analyses and Precision Oncology in Gastroesophageal Cancer: Forwards or Backwards? 14

R. Sundar and P. Tan

See article, p. 37

See article, p. 49

Collapsing the Tumor Ecosystem: Preventing Adaptive Response to Treatment by Inhibiting Transcription 17

A. Carugo and G.F. Draetta

See article, p. 59

Keeping Tumors Out of the MAPK Fitness Zone 20

D.F. Stern

See article, p. 74

REVIEW BET Proteins as Targets for Anticancer Treatment 24

A. Stathis and F. Bertoni

RESEARCH BRIEFS Genomic Heterogeneity as a Barrier to Precision Medicine in Gastroesophageal Adenocarcinoma 37



E. Pectasides, M.D. Stachler, S. Derks, Y. Liu, S. Maron, M. Islam, L. Alpert, H. Kwak, H. Kindler, B. Polite, M.R. Sharma, K. Allen, E. O'Day, S. Lomnicki, M. Maranto, R. Kanteti, C. Fitzpatrick, C. Weber, N. Setia, S.-Y. Xiao, J. Hart, R.J. Nagy, K.-M. Kim, M.-G. Choi, B.-H. Min, K.S. Nason, L. O'Keefe, M. Watanabe, H. Baba, R. Lanman, A.T. Agoston, D.J. Oh, A. Dunford, A.R. Thorner, M.D. Ducar, B.M. Wollison, H.A. Coleman, Y. Ji, M.C. Posner, K. Roggin, K. Turaga, P. Chang, K. Hogarth, U.D. Siddiqui, A. Gelrud, G. Ha, S.S. Freeman, J. Rhoades, S. Reed, G. Gydush, D. Rotem, J. Davison, Y. Imamura, V. Adalsteinsson, J. Lee, A.J. Bass, and D.V. Catenacci

Précis: Heterogeneity of actionable genomic alterations among primary and metastatic lesions suggests that biomarker profiling of a single primary tumor site may limit the success of targeted therapy in gastroesophageal adenocarcinoma.

See commentary, p. 14

See article, p. 49

Genetic Predictors of Response to Systemic Therapy in Esophagogastric Cancer 49

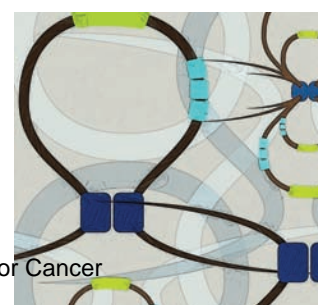
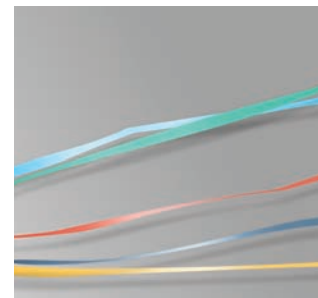
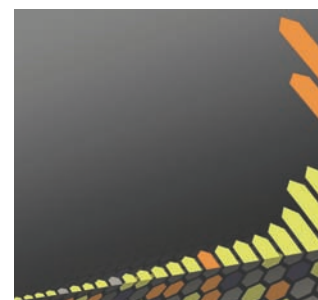
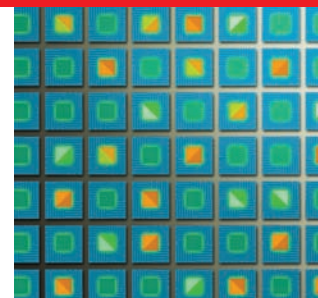


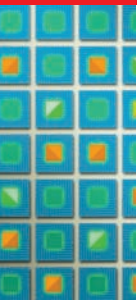
Y.Y. Janjigian, F. Sanchez-Vega, P. Jonsson, W.K. Chatila, J.F. Hechtman, G.Y. Ku, J.C. Riches, Y. Tuvy, R. Kundra, N. Bouvier, E. Vakiani, J. Gao, Z.J. Heins, B.E. Gross, D.P. Kelsen, L. Zhang, V.E. Strong, M. Schattner, H. Gerdes, D.G. Coit, M. Bains, Z.K. Stadler, V.W. Rusch, D.R. Jones, D. Molena, J. Shia, M.E. Robson, M. Capanu, S. Middha, A. Zehir, D.M. Hyman, M. Scaltriti, M. Ladanyi, N. Rosen, D.H. Ilson, M.F. Berger, L. Tang, B.S. Taylor, D.B. Solit, and N. Schultz

Précis: Prospective genomic profiling of patients with esophagogastric cancer identifies predictive biomarkers of sensitivity and resistance to trastuzumab and immune checkpoint inhibitors.

See commentary, p. 14

See article, p. 37





Suppression of Adaptive Responses to Targeted Cancer Therapy by Transcriptional Repression59

M. Rusan, K. Li, Y. Li, C.L. Christensen, B.J. Abraham, N. Kwiatkowski, K.A. Buczkowski, B. Bockorny, T. Chen, S. Li, K. Rhee, H. Zhang, W. Chen, H. Terai, T. Tavares, A.L. Leggett, T. Li, Y. Wang, T. Zhang, T.-J. Kim, S.-H. Hong, N. Poudel-Neupane, M. Silkes, T. Mudianto, L. Tan, T. Shimamura, M. Meyerson, A.J. Bass, H. Watanabe, N.S. Gray, R.A. Young, K.-K. Wong, and P.S. Hammerman

Précis: Blocking RNA polymerase II-mediated transcription with a CDK7/CDK12 inhibitor broadly enhances the efficacy of targeted therapies by suppressing transcriptional responses associated with establishment of a drug-tolerant state.


See commentary, p. 17

Conversion of PRPS Hexamer to Monomer by AMPK-Mediated Phosphorylation Inhibits Nucleotide Synthesis in Response to Energy Stress94

X. Qian, X. Li, L. Tan, J.-H. Lee, Y. Xia, Q. Cai, Y. Zheng, H. Wang, P.L. Lorenzi, and Z. Lu

Précis: Inhibition of phosphoribosyl pyrophosphate synthetase (PRPS) by AMPK under glucose-deprived or hypoxic conditions maintains homeostasis and promotes tumor cell survival.


Somatic Superenhancer Duplications and Hotspot Mutations Lead to Oncogenic Activation of the KLF5 Transcription Factor 108

 X. Zhang, P.S. Choi, J.M. Francis, G.F. Gao, J.D. Campbell, A. Ramachandran, Y. Mitsuishi, G. Ha, J. Shih, F. Vazquez, A. Tsherniak, A.M. Taylor, J. Zhou, Z. Wu, A.C. Berger, M. Giannakis, W.C. Hahn, A.D. Cherniack, and M. Meyerson

Précis: Varied noncoding and coding alterations observed across multiple cancer types converge to increase KLF5 activity and create a potential therapeutic vulnerability.

RESEARCH ARTICLES

Exploiting Drug Addiction Mechanisms to Select against MAPKi-Resistant Melanoma74

 A. Hong, G. Moriceau, L. Sun, S. Lomeli, M. Piva, R. Damoiseaux, S.L. Holmen, N.E. Sharpless, W. Hugo, and R.S. Lo

Précis: Treatment discontinuation sensitizes MAPK inhibitor-resistant melanoma to PARP inhibition and augments a cell death-predominant drug-addiction phenotype.

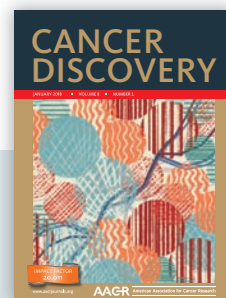
See commentary, p. 20

 AC icon indicates AuthorChoice

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

ON THE COVER

To determine how melanomas that have adapted and become addicted to MAPK inhibitors (MAPKi) respond to MAPKi withdrawal, Hong, Moriceau, and colleagues characterized the phenotypes of MAPKi-resistant melanoma cell lines after drug withdrawal. MAPKi-resistant cell lines exhibited either a cell death-predominant drug addiction phenotype characterized by ERK hyperactivation and DNA damage, or a slow cycling-predominant drug addiction phenotype. DNA damage-induced PARP1-dependent cell death was essential for the cell death-predominant phenotype, and DNA damage repair inhibitors such as PARPi induced apoptosis in cell death-predominant melanoma cell lines and caused slow cycling-predominant melanoma cell lines to switch to a cell death-predominant phenotype. Combined PARPi and vemurafenib treatment induced MAPKi-addicted tumor regression after MAPKi withdrawal. These findings identify a therapeutically exploitable mechanism driving MAPKi addiction in melanoma. For details, please see the article by Hong, Moriceau, and colleagues on page 74.



CANCER DISCOVERY

8 (1)

Cancer Discov 2018;8:OF7-125.

Updated version Access the most recent version of this article at:
<http://cancerdiscovery.aacrjournals.org/content/8/1>

E-mail alerts [Sign up to receive free email-alerts](#) related to this article or journal.

Reprints and Subscriptions To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions To request permission to re-use all or part of this article, use this link <http://cancerdiscovery.aacrjournals.org/content/8/1>. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.