

CANCER DISCOVERY CONTENTS

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IN THIS ISSUE	Highlighted research articles.....1103
NEWS IN BRIEF	Important news stories affecting the community..... 1108
NEWS IN DEPTH	A New Era in CLL Treatment 1112
RESEARCH WATCH	Selected highlights of recent articles of exceptional significance from the cancer literature 1113
ONLINE	For more News and Research Watch, visit <i>Cancer Discovery</i> online at http://CDnews.aacrjournals.org .
VIEW	In The Spotlight
	Testing the Metal of ERCC2 in Predicting the Response to Platinum-Based Therapy 1118 J.J. Turchi, D.S. Woods, and P. VanderVere-Carozza <i>See article, p. 1140</i>
	Understanding and Targeting Alkylator Resistance in Glioblastoma 1120 W. Wick and M. Platten <i>See article, p. 1198</i>
	A CREB1-TGFβ2 Self-Sustaining Loop in Glioblastoma 1123 D. Wotton <i>See article, p. 1230</i>
REVIEW	Beyond DNA Repair: DNA-PK Function in Cancer 1126 J.F. Goodwin and K.E. Knudsen

RESEARCH ARTICLES

Somatic ERCC2 Mutations Correlate with Cisplatin Sensitivity in Muscle-Invasive Urothelial Carcinoma



E.M. Van Allen, K.W. Mouw, P. Kim, G. Iyer, N. Wagle, H. Al-Ahmadie, C. Zhu, I. Ostrovskaya, G.V. Kryukov, K.W. O'Connor, J. Sfakianos, I. Garcia-Grossman, J. Kim, E.A. Guancial, R. Bambury, S. Bahl, N. Gupta, D. Farlow, A. Qu, S. Signoretti, J.A. Barletta, V. Reuter, J. Boehm, M. Lawrence, G. Getz, P. Kantoff, B.H. Bochner, T.K. Choueiri, D.F. Bajorin, D.B. Solit, S. Gabriel, A. D'Andrea, L.A. Garraway, and J.E. Rosenberg

Précis: *ERCC2* is somatically mutated in patients with urothelial carcinoma who exhibit complete response to cisplatin, and may be a predictive biomarker of clinical benefit from neoadjuvant chemotherapy.

See commentary, p. 1118

Discovery of Biomarkers Predictive of GSI Response in Triple-Negative Breast Cancer and Adenoid Cystic Carcinoma

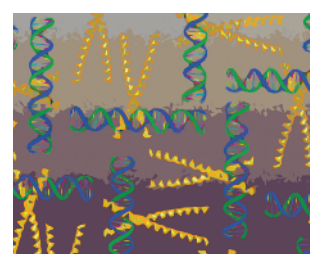
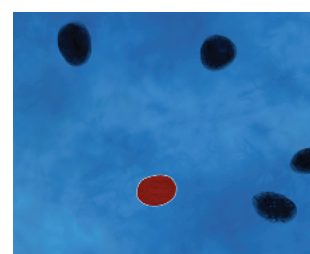
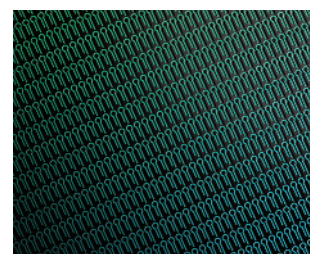
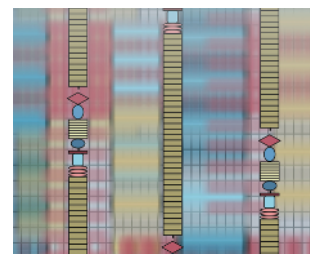
A. Stoeck, S. Lejnine, A. Truong, L. Pan, H. Wang, C. Zang, J. Yuan, C. Ware, J. MacLean, P.W. Garrett-Engele, M. Kluk, J. Laskey, B.B. Haines, C. Moskaluk, L. Zawel, S. Fawell, G. Gilliland, T. Zhang, B.E. Kremer, B. Knoechel, B.E. Bernstein, W.S. Pear, X.S. Liu, J.C. Aster, and S. Sathyanarayanan

Précis: High levels of activated NOTCH1 and expression of the target gene *HES4* are correlated with a robust response to NOTCH pathway inhibition with gamma-secretase inhibitors in *NOTCH1*-mutant tumors.

A Large-Scale RNAi-Based Mouse Tumorigenesis Screen Identifies New Lung Cancer Tumor Suppressors That Repress FGFR Signaling

L. Lin, L. Chamberlain, M.L. Pak, A. Nagarajan, R. Gupta, L.J. Zhu, C.M. Wright, K.M. Fong, N. Wajapeyee, and M.R. Green

Précis: An shRNA-based functional screen identified transcriptionally silenced candidate tumor suppressor genes that are downregulated in human lung squamous cell carcinoma, many of which inhibit FGFR signaling.



Development of siRNA Payloads to Target KRAS-Mutant Cancer 1182

T.L. Yuan, C. Fellmann, C.-S. Lee, C.D. Ritchie, V. Thapar, L.C. Lee, D.J. Hsu, D. Grace, J.O. Carver, J. Zuber, J. Luo, F. McCormick, and S.W. Lowe

Précis: An RNAi library of potent siRNAs facilitates low-dose, combinatorial gene knockdown of KRAS and RAS pathway effector nodes and inhibits KRAS-mutant colorectal cancer growth.

ATM Regulates 3-Methylpurine-DNA Glycosylase and Promotes Therapeutic Resistance to Alkylating Agents . . . 1198

AC S. Agnihotri, K. Burrell, P. Buczkowicz, M. Remke, B. Golbourn, Y. Chornenkyy, A. Gajadhar, N.A. Fernandez, I.D. Clarke, M.S. Barszczyk, S. Pajovic, C. Ternamian, R. Head, N. Sabha, R.W. Sobol, M.D. Taylor, J.T. Rutka, C. Jones, P.B. Dirks, G. Zadeh, and C. Hawkins

Précis: ATM can promote temozolomide resistance in pediatric glioblastoma by activating 3-methylpurine-DNA glycosylase (MPG)-mediated base excision repair.

See commentary, p. 1120

The Immune Microenvironment Confers Resistance to MAPK Pathway Inhibitors through Macrophage-Derived TNF α 1214

AC M.P. Smith, B. Sanchez-Laorden, K. O'Brien, H. Brunton, J. Ferguson, H. Young, N. Dhomen, K.T. Flaherty, D.T. Frederick, Z.A. Cooper, J.A. Wargo, R. Marais, and C. Wellbrock

Précis: TNF α expressed in tumor-associated macrophages promotes MAPK pathway inhibitor resistance in melanoma, which can be overcome by combined treatment with I κ B kinase inhibitors.

Active CREB1 Promotes a Malignant TGF β 2 Autocrine Loop in Glioblastoma 1230

L. Rodón, A. González-Juncà, M. del Mar Inda, A. Sala-Hojman, E. Martínez-Sáez, and J. Seoane

Précis: TGF β activates CREB1- and SMAD3-dependent *TGFB2* transcription and hyperactivation of TGF β signaling in human glioblastoma cell lines and tumors.

See commentary, p. 1123

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ON THE COVER

Smith, Sanchez-Laorden, and colleagues found that macrophage-derived TNF α was required for *BRAF*^{V600E}-positive melanoma cell survival and protected these cells from MEK inhibitor (MEKi)-induced cell death via NF κ B-dependent upregulation of microphthalmia-associated transcription factor (MITF). MEK/BRAF inhibitor treatment increased tumor-associated macrophage recruitment and TNF α and MITF expression in *BRAF*-mutant melanomas. Intriguingly, dual treatment with I κ B kinase inhibitors (IKKi) and MEKi suppressed both macrophage-derived TNF α expression and MITF expression in melanoma cells and resulted in enhanced inhibition of tumor growth in mice. These findings highlight the role of the immune microenvironment in MAPK inhibitor resistance and suggest that IKKi therapy may improve the efficacy of MAPK pathway inhibitors by preventing TNF α -mediated resistance. For details, please see the article by Smith, Sanchez-Laorden, and colleagues on page 1214.



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