

CANCER DISCOVERY CONTENTS

FEBRUARY 2018 ■ VOLUME 8 ■ NUMBER 2

IN THIS ISSUE Highlighted research articles 127

NEWS IN BRIEF Important news stories affecting the community 130

NEWS IN DEPTH Gut Bacteria Shape Therapeutic Response 134

RESEARCH WATCH Selected highlights of recent articles of exceptional significance from the cancer literature 135

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

IEWS In The Spotlight

ERK Inhibition: A New Front in the War against MAPK Pathway-Driven Cancers? 140
I. Smalley and K.S.M. Smalley
See article, p. 184

A Critical Need for Better Cancer Immunotherapy Models: Are Organotypic Tumor Spheroid Cultures the Answer? 143
J.M. Balko and J.A. Sosman
See article, p. 196
See article, p. 216

What's the FOX Got to Do with the KITten? Regulating the Lineage-Specific Transcriptional Landscape in GIST 146
D.M. Lee and A. Duensing
See article, p. 234

REVIEW The Expanding World of N-MYC-Driven Tumors 150
AC D.S. Rickman, J.H. Schulte, and M. Eilers

RESEARCH BRIEFS Genomic Landscape of Cell-Free DNA in Patients with Colorectal Cancer 164

AC J.H. Strickler, J.M. Loree, L.G. Ahronian, A.R. Parikh, D. Niedzwiecki, A.A.L. Pereira, M. McKinney, W.M. Korn, C.E. Atreya, K.C. Banks, R.J. Nagy, F. Meric-Bernstam, R.B. Lanman, A. Talasz, I.F. Tsigelny, R.B. Corcoran, and S. Kopetz

Précis: cfDNA profiling has high concordance with direct tumor sequencing in 1,397 patients with advanced colorectal cancer and uncovers *EGFR* ECD mutations that may drive resistance to anti-*EGFR* antibodies.

Accelerating Discovery of Functional Mutant Alleles in Cancer 174

AC M.T. Chang, T.S. Bhattarai, A.M. Schram, C.M. Bielski, M.T.A. Donoghue, P. Jonsson, D. Chakravarty, S. Phillips, C. Kandoth, A. Penson, A. Gorelick, T. Shamu, S. Patel, C. Harris, J. Gao, S.O. Sumer, R. Kundra, P. Razavi, B.T. Li, D.N. Reales, N.D. Socci, G. Jayakumar, A. Zehir, R. Benayed, M.E. Arcila, S. Chandralapaty, M. Ladanyi, N. Schultz, J. Baselga, M.F. Berger, N. Rosen, D.B. Solit, D.M. Hyman, and B.S. Taylor

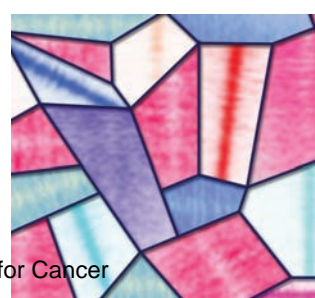
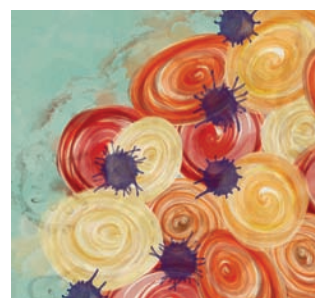
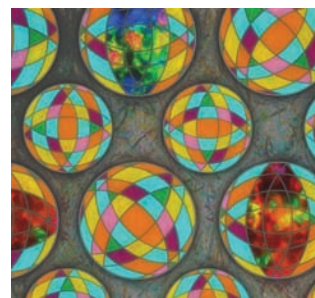
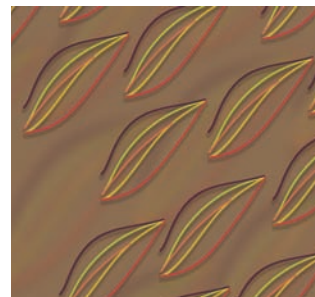
Précis: Analysis of somatic mutational data in large patient cohorts uncovered rare hotspots that may accelerate the discovery of rare driver mutations in cancer and guide selection of targeted therapies.

RESEARCH ARTICLES First-in-Class ERK1/2 Inhibitor Ulixertinib (BVD-523) in Patients with MAPK Mutant Advanced Solid Tumors: Results of a Phase I Dose-Escalation and Expansion Study 184

AC R.J. Sullivan, J.R. Infante, F. Janku, D.J.L. Wong, J.A. Sosman, V. Keedy, M.R. Patel, G.I. Shapiro, J.W. Mier, A.W. Tolcher, A. Wang-Gillam, M. Sznol, K. Flaherty, E. Buchbinder, R.D. Carvajal, A.M. Varghese, M.E. Lacouture, A. Ribas, S.P. Patel, G.A. DeCrescenzo, C.M. Emery, A.L. Groover, S. Saha, M. Varterasian, D.J. Welsch, D.M. Hyman, and B.T. Li

Précis: The ERK inhibitor ulixertinib is well tolerated and achieved partial responses in patients with *NRAS*-, *BRAF*^{V600}-, and non-V600 *BRAF*-mutant advanced solid tumors in a phase I clinical trial.

See commentary, p. 140






Ex Vivo Profiling of PD-1 Blockade Using Organotypic Tumor Spheroids 196

R.W. Jenkins, A.R. Aref, P.H. Lizotte, E. Ivanova, S. Stinson, C.W. Zhou, M. Bowden, J. Deng, H. Liu, D. Miao, M.X. He, W. Walker, G. Zhang, T. Tian, C. Cheng, Z. Wei, S. Palakurthi, M. Bittinger, H. Vitzthum, J.W. Kim, A. Merlino, M. Quinn, C. Venkataramani, J.A. Kaplan, A. Portell, P.C. Gokhale, B. Phillips, A. Smart, A. Rotem, R.E. Jones, L. Keogh, M. Anguiano, L. Stapleton, Z. Jia, M. Barzily-Rokni, I. Cañadas, T.C. Thai, M.R. Hammond, R. Vlahos, E.S. Wang, H. Zhang, S. Li, G.J. Hanna, W. Huang, M.P. Hoang, A. Piris, J.-P. Eliane, A.O. Stemmer-Rachamimov, L. Cameron, M.-J. Su, P. Shah, B. Izar, M. Thakuria, N.R. LeBoeuf, G. Rabinowits, V. Gunda, S. Parangi, J.M. Cleary, B.C. Miller, S. Kitajima, R. Thummalapalli, B. Miao, T.U. Barbie, V. Sivathanu, J. Wong, W.G. Richards, R. Bueno, C.H. Yoon, J. Miret, M. Herlyn, L.A. Garraway, E.M. Van Allen, G.J. Freeman, P.T. Kirschmeier, J.H. Lorch, P.A. Ott, F.S. Hodi, K.T. Flaherty, R.D. Kamm, G.M. Boland, K.-K. Wong, D. Dornan, C.P. Paweletz, and D.A. Barbie

Précis: Mouse- and patient-derived organotypic tumor spheroids model the tumor-immune microenvironment to predict response and resistance to anti-PD-1 and evaluate potential combination therapies.

See commentary, p. 143
See article, p. 216

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CDK4/6 Inhibition Augments Antitumor Immunity by Enhancing T-cell Activation... 216

J. Deng, E.S. Wang, R.W. Jenkins, S. Li, R. Dries, K. Yates, S. Chhabra, W. Huang, H. Liu, A.R. Aref, E. Ivanova, C.P. Paweletz, M. Bowden, C.W. Zhou, G.S. Herter-Sprie, J.A. Sorrentino, J.E. Bisi, P.H. Lizotte, A.A. Merlino, M.M. Quinn, L.E. Bufe, A. Yang, Y. Zhang, H. Zhang, P. Gao, T. Chen, M.E. Cavanaugh, A.J. Rode, E. Haines, P.J. Roberts, J.C. Strum, W.G. Richards, J.H. Lorch, S. Parangi, V. Gunda, G.M. Boland, R. Bueno, S. Palakurthi, G.J. Freeman, J. Ritz, W.N. Haining, N.E. Sharpless, H. Arthanari, G.I. Shapiro, D.A. Barbie, N.S. Gray, and K.-K. Wong

Précis: CDK4/6 inhibitors derepress NFAT to promote IL2 secretion, enhance T-cell activation and tumor infiltration, and cooperate with anti-PD-1 antibodies to boost antitumor immunity *in vivo*.

See commentary, p. 143
See article, p. 196

FOXF1 Defines the Core-Regulatory Circuitry in Gastrointestinal Stromal Tumor 234

L. Ran, Y. Chen, J. Sher, E.W.P. Wong, D. Murphy, J.Q. Zhang, D. Li, K. Deniz, I. Sirota, Z. Cao, S. Wang, Y. Guan, S. Shukla, K.Y. Li, A. Chramiec, Y. Xie, D. Zheng, R.P. Koche, C.R. Antonescu, Y. Chen, and P. Chi

Précis: Gastrointestinal stromal tumors exhibit a transcriptional dependence on FOXF1, which binds enhancers to promote expression of genes, including *ETV1* and *KIT*, required for tumor growth.

See commentary, p. 146

ON THE COVER

Deng, Wang, Jenkins, and colleagues found that cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors augment PD-1 blockade by increasing the activity of PD-1 overexpressing T cells. CDK4/6 inhibition relieved NFAT suppression by preventing CDK6-mediated NFAT phosphorylation, thereby promoting NFAT signaling, IL2 secretion, and T-cell activity. *In vivo*, CDK4/6 inhibition enhanced T-cell tumor infiltration despite reducing T-cell proliferation, and CDK4/6 inhibitors cooperated with anti-PD-1 therapy to induce T cell-mediated antitumor immunity, synergizing with PD-1 blocking antibodies in multiple syngeneic tumor models. These results describe a mechanism by which CDK4/6 inhibitors may promote T-cell activity and improve the efficacy of anti-PD-1 therapy, suggesting that combined treatment with CDK4/6 inhibitors and immune checkpoint blockade may be beneficial in patients with cancer. For details, please see the article by Deng, Wang, Jenkins, and colleagues on page 216.



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8 (2)

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