

# CANCER DISCOVERY CONTENTS

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**REVIEW** The Expanding World of N-MYC-Driven Tumors ..... 150  
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**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

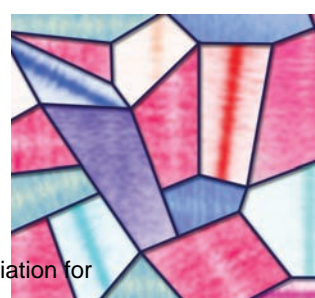
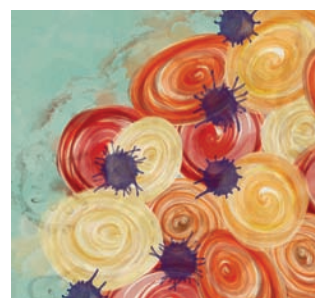
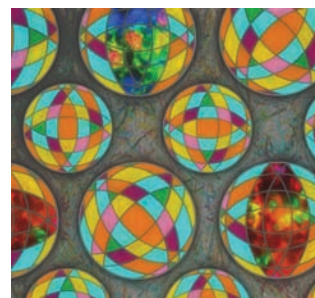
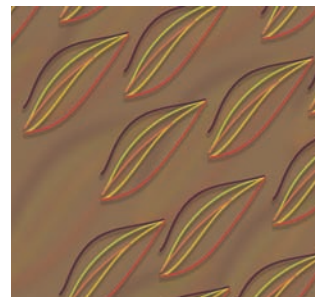
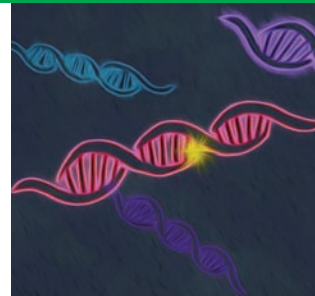
**Précis:** Analysis of somatic mutational data in large patient cohorts uncovered rare hotspots that may accelerate the discovery of rare driver mutations in cancer and guide selection of targeted therapies.

**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*<sup>V600-</sup>, 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. Rabinowitz, 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**

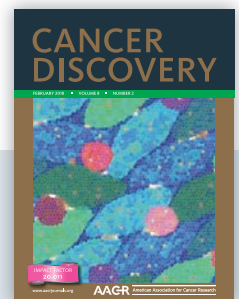
L. Ran, Y. Chen, J. Sher, E.W.P. Wong, D. Murphy, J.Q. Zhang, D. Li, K. Deniz, I. Sirota, Z. Cao, S. Wang, Y. Guan, S. Shukla, K.Y. Li, A. Chramiec, Y. Xie, D. Zheng, R.P. Koche, C.R. Antonescu, Y. Chen, and P. Chi

**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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