

CANCER DISCOVERY CONTENTS

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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.

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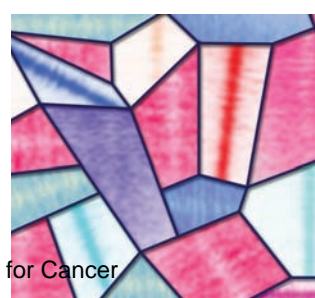
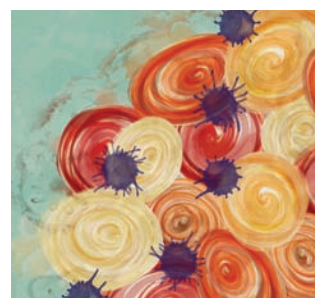
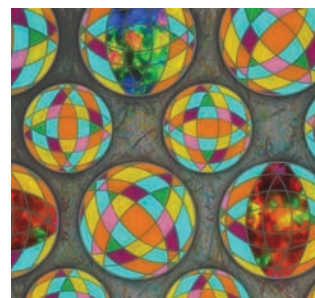
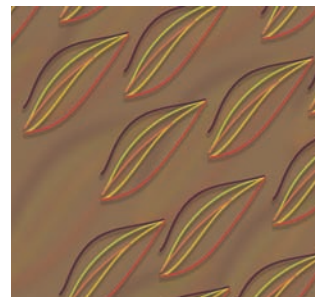
Précis: Analysis of somatic mutational data in large patient cohorts uncovered rare hotspots that may accelerate the discovery of rare driver mutations in cancer and guide selection of targeted therapies.

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

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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.

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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.

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 AC icon indicates AuthorChoice

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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*.

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

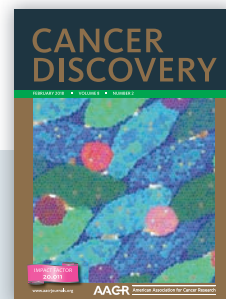
L. Ran, Y. Chen, J. Sher, E.W.P. Wong, D. Murphy, J.Q. Zhang, D. Li, K. Deniz, I. Sirota, Z. Cao, S. Wang, Y. Guan, S. Shukla, K.Y. Li, A. Chramiec, Y. Xie, D. Zheng, R.P. Koche, C.R. Antonescu, Y. Chen, and P. Chi

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.

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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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