

CANCER DISCOVERY

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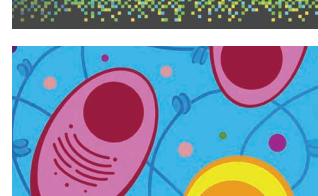
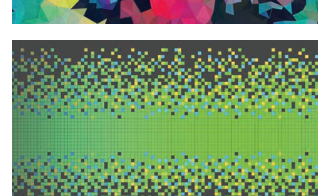
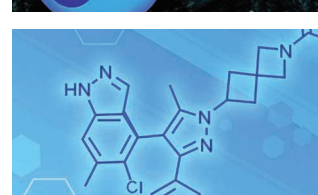
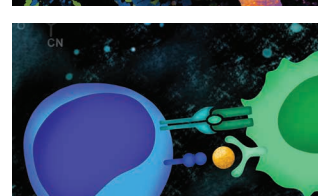
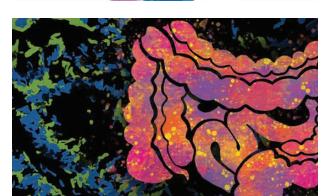
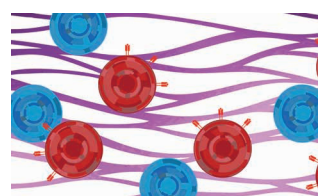
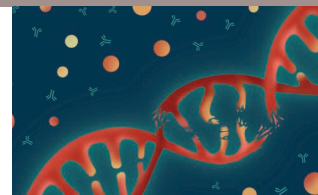
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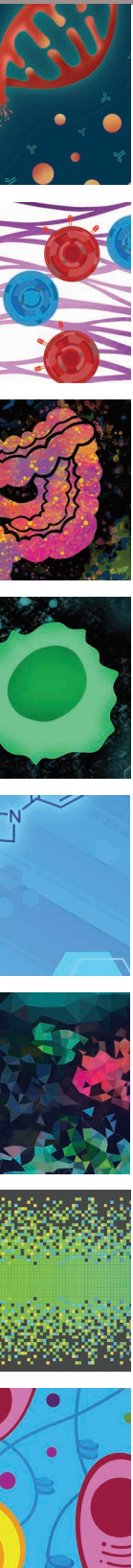
R. Martini, E. Gebregzabher, L. Newman, and M.B. Davis

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Précis: Mutations leading to POLE proof-reading deficiency contribute to high tumor burden and predict efficacy of anti-PD-1 therapy in patients with mismatch repair-proficient tumors, suggesting their potential use as a biomarker of cancer immunotherapy response.





Integrated Multiomic Profiling Identifies the Epigenetic Regulator PRC2 as a Therapeutic Target to Counteract Leukemia Immune Escape and Relapse1449

V. Gambacorta, S. Beretta, M. Ciccimarra, L. Zito, K. Giannetti, A. Andrisani, D. Gnani, L. Zanotti, G. Oliveira, M.G. Carrabba, D. Cittaro, I. Merelli, F. Ciceri, R. Di Micco, and L. Vago

Précis: The chromatin repressor PRC2 induces HLA class II silencing in acute myeloid leukemia leading to immune escape and posttransplantation relapse, while its chemical inhibition rescues HLA expression and triggers T cell-mediated leukemia eradication.

See commentary, p. 1410

RESEARCH ARTICLES

Reverse Transcriptase Inhibition Disrupts Repeat Element Life Cycle in Colorectal Cancer 1462

M. Rajurkar, A.R. Parikh, A. Solovyov, E. You, A.S. Kulkarni, C. Chu, K.H. Xu, C. Jaicks, M.S. Taylor, C. Wu, K.A. Alexander, C.R. Good, A. Szabolcs, S. Gerstberger, A.V. Tran, N. Xu, R.Y. Ebricht, E.E. Van Seventer, K.D. Vo, E.C. Tai, C. Lu, J. Joseph-Chazan, M.J. Raabe, L.T. Nieman, N. Desai, K.S. Arora, M. Ligorio, V. Thapar, L. Cohen, P.M. Garden, Y. Senussi, H. Zheng, J.N. Allen, L.S. Blaszkowsky, J.W. Clark, L. Goyal, J.Y. Wo, D.P. Ryan, R.B. Corcoran, V. Deshpande, M.N. Rivera, M.J. Aryee, T.S. Hong, S.L. Berger, D.R. Walt, K.H. Burns, P.J. Park, B.D. Greenbaum, and D.T. Ting

Précis: Colorectal cancers express abundant viral-like repeat elements that can be targeted by nucleoside reverse transcriptase inhibitors in preclinical models, which was further translated into a phase II clinical trial.

Characterization of INCB086550: A Potent and Novel Small-Molecule PD-L1 Inhibitor 1482

H.K. Koblisch, L. Wu, L.-C.S. Wang, P.C.C. Liu, R. Wynn, J. Rios-Doria, S. Spitz, H. Liu, A. Volgina, N. Zolotarjova, K. Kapilashrami, E. Behshad, M. Covington, Y.-o. Yang, J. Li, S. Diamond, M. Soloviev, K. O'Hayer, S. Rubin, C. Kanellopoulou, G. Yang, M. Rupar, D. DiMatteo, L. Lin, C. Stevens, Y. Zhang, P. Thekkat, R. Geschwindt, C. Marando, S. Yelleswaram, J. Jackson, P. Scherle, R. Huber, W. Yao, and G. Hollis

Précis: Development and characterization of INCB086550, a potent, selective, and orally bioavailable small-molecule inhibitor of PD-L1, showed antitumor efficacy and represents a new modality to block the PD-L1/PD-1 interaction.

See commentary, p. 1413

Discovery, Preclinical Characterization, and Early Clinical Activity of JDQ443, a Structurally Novel, Potent, and Selective Covalent Oral Inhibitor of KRAS^{G12C} 1500

A. Weiss, E. Lorthiois, L. Barys, K.S. Beyer, C. Bomio-Confaglia, H. Burks, X. Chen, X. Cui, R. de Kanter, L. Dharmarajan, C. Fedele, M. Gerspacher, D.A. Guthy, V. Head, A. Jaeger, E. Jiménez Núñez, J.D. Kearns, C. Leblanc, S.-M. Maira, J. Murphy, H. Oakman, N. Ostermann, J. Ottl, P. Rigollier, D. Roman, C. Schnell, R. Sedrani, T. Shimizu, R. Stringer, A. Vaupel, H. Voshol, P. Wessels, T. Widmer, R. Wilcken, K. Xu, F. Zecri, A.F. Farago, S. Costesa, and S.M. Brachmann

Précis: The structurally unique KRAS^{G12C} inhibitor JDQ443 shows potent, mutant-selective antitumor activity in preclinical models as well as in patients, both alone and in combination with the SHP2 inhibitor TNO155.

The Spatial Landscape of Progression and Immunoediting in Primary Melanoma at Single-Cell Resolution 1518

A.J. Nirmal, Z. Maliga, T. Vallius, B. Quattrochi, A.A. Chen, C.A. Jacobson, R.J. Pelletier, C. Yapp, R. Arias-Camison, Y.-A. Chen, C.G. Lian, G.F. Murphy, S. Santagata, and P.K. Sorger

Précis: Spatial profiling of cutaneous melanoma at the single-cell level provided molecular features of progression and immunosuppression, which include paracrine cytokine signaling and direct immune cell-cell contact.

Precision Combination Therapies Based on Recurrent Oncogenic Coalterations 1542

X. Li, E.K. Dowling, G. Yan, Z. Dereli, B. Bozorgui, P. Imanirad, J.H. Elnaggar, A. Luna, D.G. Menter, P.G. Pilié, T.A. Yap, S. Kopetz, C. Sander, and A. Korkut

Précis: The REFLECT platform was developed and allows for the identification of targetable coalterations in patient cohorts, with its use in preclinical and clinical settings demonstrating improvements to efficacy and survival.

See commentary, p. 1416

Epigenetic Activation of Plasmacytoid DCs Drives IFNAR-Dependent Therapeutic Differentiation of AML... 1560

J.M. Salmon, I. Todorovski, K.L. Stanley, C. Bruedigam, C.J. Kearney, L.G. Martelotto, F. Rossello, T. Semple, G. Mir Arnau, M. Zethoven, M. Bots, S. Bjelosevic, L.A. Cluse, P.J. Fraser, V. Litalien, E. Vidacs, K. McArthur, A.Y. Matthews, E. Gressier, N.A. de Weerd, J. Lichte, M.J. Kelly, S.J. Hogg, P.J. Hertzog, L.M. Kats, S.J. Vervoort, D.D. De Carvalho, S. Scheu, S. Bedoui, B.T. Kile, S.W. Lane, A.C. Perkins, A.H. Wei, P.M. Dominguez, and R.W. Johnstone

Précis: Type I IFN produced by plasmacytoid dendritic cells in response to histone deacetylase inhibition is required to induce differentiation of leukemia cells and ultimately tumor cell death in acute myeloid leukemia.

Identification of Functional Heterogeneity of Carcinoma-Associated Fibroblasts with Distinct IL6-Mediated Therapy Resistance in Pancreatic Cancer... 1580

K.M. McAndrews, Y. Chen, J.K. Darpolor, X. Zheng, S. Yang, J.L. Carstens, B. Li, H. Wang, T. Miyake, P. Correa de Sampaio, M.L. Kirtley, M. Natale, C.-C. Wu, H. Sugimoto, V.S. LeBleu, and R. Kalluri

Précis: Heterogeneity in the function of carcinoma-associated fibroblasts (CAF) indicated that IL6 depletion from only the α SMA⁺ CAF subtype led to improvement in gemcitabine response in patients with pancreatic cancer.

Correction

Correction: Efficacy and Safety of Patritumab Deruxtecan (HER3-DXd) in EGFR Inhibitor-Resistant, EGFR-Mutated Non-Small Cell Lung Cancer... 1598

ON THE COVER

Mutations in KRAS span many cancer types and had been considered undruggable until the development of small-molecule inhibitors of the KRAS^{G12C} mutant protein. Several covalent inhibitors targeting this mutation have entered clinical development and have demonstrated antitumor activity; however, acquired resistance has emerged, and combination strategies have been suggested. Weiss, Lorthiois, and colleagues developed JDQ443, a structurally unique, potent, and covalent KRAS^{G12C} inhibitor capable of inhibiting downstream signaling and proliferation, including in KRAS^{G12C}-mutant cells with secondary KRAS mutations associated with KRAS^{G12C} inhibitor resistance, and with antitumor activity in preclinical models as both a monotherapy and in combination with inhibitors of SHP2, MEK1/2, and CDK4/6. Clinical activity was also demonstrated for JDQ443 both alone and in combination with the SHP2 inhibitor TNO155 in patients with KRAS^{G12C} mutations. For more information, see the article by Weiss, Lorthiois, and colleagues on page 1500.

doi: 10.1158/2159-8290.CD-12-6-CVR

