

IN THIS ISSUE Highlighted research articles 983

NEWS IN BRIEF Important news stories affecting the community 988

NEWS IN DEPTH IDH Inhibitors Target Common Glioma Mutation 992

RESEARCH WATCH Selected highlights of recent articles of exceptional significance from the cancer literature 993

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VIEWS In The Spotlight

Polyclonal Heterogeneity: The New Norm for Secondary Clinical Resistance to Targeted Monotherapy in Relapsed Leukemia? 998

A.H. Wei and A.W. Roberts

See article, p. 1050

A Single-Cell Window into Pancreas Cancer Fibroblast Heterogeneity 1001

J.I. Belle and D.G. DeNardo

See article, p. 1102

Immune Desertic Landscapes in Hepatocellular Carcinoma Shaped by β -Catenin Activation 1003

P. Berraondo, M.C. Ochoa, I. Olivera, and I. Melero

See article, p. 1124

REVIEW The Metabolic Basis of Kidney Cancer 1006

W.M. Linehan, L.S. Schmidt, D.R. Crooks, D. Wei, R. Srinivasan, M. Lang, and C.J. Ricketts

RESEARCH BRIEF

Unique Neoantigens Arise from Somatic Mutations in Patients with Gastrointestinal Cancers 1022

M.R. Parkhurst, P.F. Robbins, E. Tran, T.D. Prickett, J.J. Gartner, L. Jia, G. Ivey, Y.F. Li, M. El-Gamil, A. Lalani, J.S. Crystal, A. Sachs, E. Groh, S. Ray, L.T. Ngo, S. Kivitz, A. Pasetto, R. Yossef, F.J. Lowery, S.L. Goff, W. Lo, G. Cafri, D.C. Deniger, P. Malekzadeh, M. Ahmadzadeh, J.R. Wunderlich, R.P.T. Somerville, and S.A. Rosenberg

Précis: Neoantigens in cancers with low numbers of mutations are similarly recognized by tumor-infiltrating lymphocytes, with implications for improving immunotherapy.

RESEARCH ARTICLES

First-in-Human RNA Polymerase I Transcription Inhibitor CX-5461 in Patients with Advanced Hematologic Cancers: Results of a Phase I Dose-Escalation Study 1036



A. Khot, N. Brajanovski, D.P. Cameron, N. Hein, K.H. MacLachlan, E. Sanij, J. Lim, J. Soong, E. Link, P. Blombery, E.R. Thompson, A. Fellowes, K.E. Sheppard, G.A. McArthur, R.B. Pearson, R.D. Hannan, G. Poortinga, and S.J. Harrison

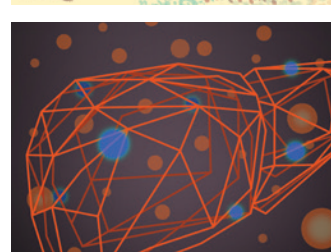
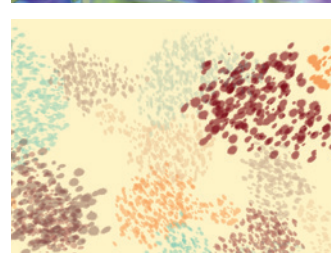
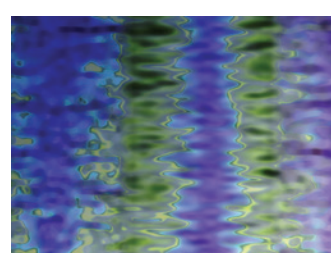
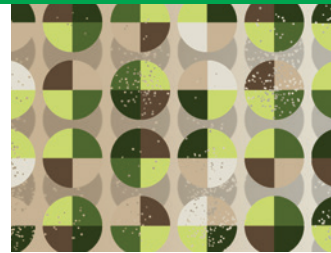
Précis: A phase I dose-escalation study evaluates the safety and pharmacokinetics of the RNA Polymerase I inhibitor CX-5461 in patients with advanced hematologic cancers.

Clonal Selection with RAS Pathway Activation Mediates Secondary Clinical Resistance to Selective FLT3 Inhibition in Acute Myeloid Leukemia 1050

C.M. McMahon, T. Ferng, J. Canaani, E.S. Wang, J.J.D. Morrisette, D.J. Eastburn, M. Pellegrino, R. Durruthy-Durruthy, C.D. Watt, S. Asthana, E.A. Lasater, R. DeFilippis, C.A.C. Peretz, L.H.F. McGary, S. Deihimi, A.C. Logan, S.M. Luger, N.P. Shah, M. Carroll, C.C. Smith, and A.E. Perl

Précis: Targeted next-generation sequencing of matched pretreatment and progressive samples from patients with AML on gilteritinib identified multiple secondary gilteritinib resistance mechanisms.

See commentary, p. 998





TAS-120 Overcomes Resistance to ATP-Competitive FGFR Inhibitors in Patients with FGFR2 Fusion-Positive Intrahepatic Cholangiocarcinoma 1064



L. Goyal, L. Shi, L.Y. Liu, F. Fece de la Cruz, J.K. Lennerz, S. Raghavan, I. Leschiner, L. Elagina, G. Siravegna, R.W.S. Ng, P. Vu, K.C. Patra, S.K. Saha, R.N. Uppot, R. Arellano, S. Reyes, T. Sagara, S. Otsuki, B. Nades, H.A. Shahzade, I. Dey-Guha, I.J. Fetter, I. Baiev, E.E. Van Seventer, J.E. Murphy, C.R. Ferrone, K.K. Tanabe, V. Deshpande, J.J. Harding, R. Yaeger, R.K. Kelley, A. Bardelli, A.J. Iafrate, W.C. Hahn, C.H. Benes, D.T. Ting, H. Hirai, G. Getz, D. Juric, A.X. Zhu, R.B. Corcoran, and N. Bardeesy

Précis: The irreversible FGFR inhibitor TAS-120 has clinical activity against FGFR2 mutations that confer resistance to FGFR inhibitors in patients with FGFR2-altered intrahepatic cholangiocarcinoma.

Aging Human Hematopoietic Stem Cells Manifest Profound Epigenetic Reprogramming of Enhancers That May Predispose to Leukemia 1080

E.R. Adelman, H.-T. Huang, A. Roisman, A. Olsson, A. Colaprico, T. Qin, R.C. Lindsley, R. Bejar, N. Salomonis, H.L. Grimes, and M.E. Figueroa

Précis: Human hematopoietic stem cells undergo age-associated genome-wide epigenomic changes that target developmental and cancer-related pathways and may increase susceptibility to myeloid malignancies.



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Cross-Species Single-Cell Analysis of Pancreatic Ductal Adenocarcinoma Reveals Antigen-Presenting Cancer-Associated Fibroblasts 1102

E. Elyada, M. Bolisetty, P. Laise, W.F. Flynn, E.T. Courtois, R.A. Burkhart, J.A. Teinor, P. Belleau, G. Biffi, M.S. Lucito, S. Sivajothi, T.D. Armstrong, D.D. Engle, K.H. Yu, Y. Hao, C.L. Wolfgang, Y. Park, J. Preall, E.M. Jaffee, A. Califano, P. Robson, and D.A. Tuveson

Précis: A previously unknown class of cancer-associated fibroblasts with unique immune properties may contribute to the immunosuppressive PDAC microenvironment.

See commentary, p. 1001

β -Catenin Activation Promotes Immune Escape and Resistance to Anti-PD-1 Therapy in Hepatocellular Carcinoma 1124



M. Ruiz de Galarreta, E. Bresnahan, P. Molina-Sánchez, K.E. Lindblad, B. Maier, D. Sia, M. Puigvehi, V. Miguela, M. Casanova-Acebes, M. Dhainaut, C. Villacorta-Martin, A.D. Singhi, A. Moghe, J. von Felden, L. Tal Grinspan, S. Wang, A.O. Kamphorst, S.P. Monga, B.D. Brown, A. Villanueva, J.M. Llovet, M. Merad, and A. Lujambio

Précis: A mouse model of hepatocellular carcinoma reveals that β -catenin activation leads to anti-PD-1 resistance via faulty immune surveillance.

See commentary, p. 1003

Editor's Note

Editor's Note: Increased Levels of COX-2 and Prostaglandin E2 Contribute to Elevated Aromatase Expression in Inflamed Breast Tissue of Obese Women 1142

ON THE COVER

Elyada and colleagues profiled human pancreatic ductal adenocarcinoma tumors and adjacent normal tissue along with mouse pancreatic tumors and discovered a previously unknown class of cancer-associated fibroblasts (CAF) they named antigen-presenting CAFs (apCAF). These CAFs are unique in their expression of MHC class II-related genes, which implies they may interact with CD4⁺ T cells; supporting this idea, apCAFs activated CD4⁺ T cells *ex vivo* in an antigen-dependent fashion. Also unlike other CAFs, apCAFs upregulate MYC targets and antigen presentation, antigen processing, fatty-acid metabolism, and MTORC1 signaling pathways. Hinting that apCAFs may contribute to immune suppression in PDAC, they do not produce costimulatory molecules needed for induction of T-cell proliferation. For details, please see the article by Elyada and colleagues on page 1102.

