

CANCER DISCOVERY CONTENTS

NOVEMBER 2017 ■ VOLUME 7 ■ NUMBER 11

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C.J. Ricketts and W.M. Linehan
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AC J.J. Northey, L. Przybyla, and V.M. Weaver

RESEARCH BRIEF Constitutive Signaling from an Engineered IL7 Receptor Promotes Durable Tumor Elimination by Tumor-Redirected T Cells. 1238

T. Shum, B. Omer, H. Tashiro, R.L. Kruse, D.L. Wagner, K. Parikh, Z. Yi, T. Sauer, D. Liu, R. Parihar, P. Castillo, H. Liu, M.K. Brenner, L.S. Metelitsa, S. Gottschalk, and C.M. Rooney

Précis: Expression of a constitutive IL7R in chimeric antigen receptor (CAR)-expressing T cells allows selective activation of immunostimulatory cytokine signaling and enhances CAR-T cell expansion and antitumor activity.

RESEARCH ARTICLES Recurrent Tumor Cell-Intrinsic and -Extrinsic Alterations during MAPKi-Induced Melanoma Regression and Early Adaptation 1248

AC C. Song, M. Piva, L. Sun, A. Hong, G. Moriceau, X. Kong, H. Zhang, S. Lomeli, J. Qian, C.C. Yu, R. Damoiseaux, M.C. Kelley, K.B. Dahlman, P.O. Scumpia, J.A. Sosman, D.B. Johnson, A. Ribas, W. Hugo, and R.S. Lo

Précis: Integrated analysis of melanoma tumors and patient-derived cell lines defines recurrent tumor cell-intrinsic and immune microenvironment alterations linked to early MAPK inhibitor resistance.

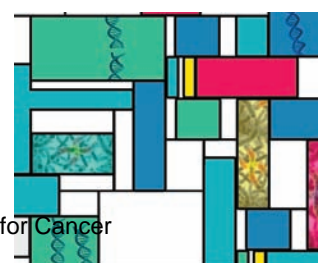
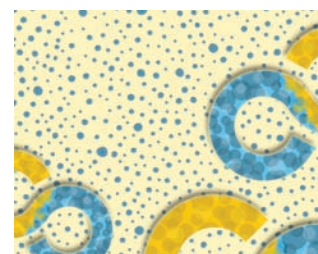
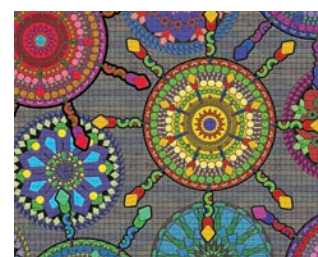
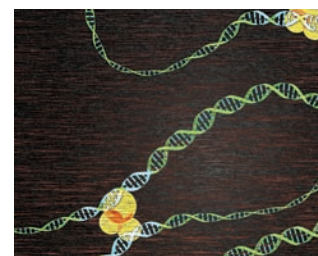
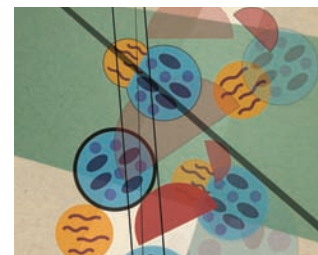
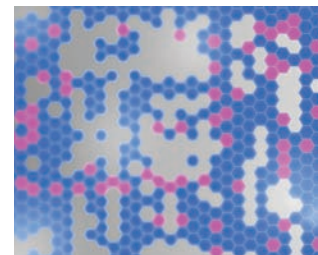
See commentary, p. 1216

A Unified Approach to Targeting the Lysosome's Degradative and Growth Signaling Roles 1266

AC V.W. Rebecca, M.C. Nicastrì, N. McLaughlin, C. Fennelly, Q. McAfee, A. Ronghe, M. Nofal, C.-Y. Lim, E. Witze, C.I. Chude, G. Zhang, G.M. Alicea, S. Piao, S. Murugan, R. Ojha, S.M. Levi, Z. Wei, J.S. Barber-Rotenberg, M.E. Murphy, G.B. Mills, Y. Lu, J. Rabinowitz, R. Marmorstein, Q. Liu, S. Liu, X. Xu, M. Herlyn, R. Zoncu, D.C. Brady, D.W. Speicher, J.D. Winkler, and R.K. Amaravadi

Précis: A screen of chloroquine compounds identifies an inhibitor of both lysosomal anabolic and catabolic functions with enhanced antitumor activity compared with existing inhibitors of catabolic function.

See commentary, p. 1218





VHL Deficiency Drives Enhancer Activation of Oncogenes in Clear Cell Renal Cell Carcinoma 1284



X. Yao, J. Tan, K.J. Lim, J. Koh, W.F. Ooi, Z. Li, D. Huang, M. Xing, Y.S. Chan, J.Z. Qu, S.T. Tay, G. Wijaya, Y.N. Lam, J.H. Hong, A.P. Lee-Lim, P. Guan, M.S.W. Ng, C.Z. He, J.S. Lin, T. Nandi, A. Qamra, C. Xu, S.S. Myint, J.O.J. Davies, J.Y. Goh, G. Loh, B.C. Tan, S.G. Rozen, Q. Yu, I.B.H. Tan, C.W.S. Cheng, S. Li, K.T.E. Chang, P.H. Tan, D.L. Silver, A. Lezhava, G. Steger, J.R. Hughes, B.T. Teh, and P. Tan

Précis: Loss of *VHL* enhances HIF2 α -HIF1 β binding at clear cell renal cell carcinoma gene enhancers, facilitating p300 recruitment and expression of lineage-specific cancer genes.

See commentary, p. 1221

Inducible Activation of MyD88 and CD40 in CAR T Cells Results in Controllable and Potent Antitumor Activity in Preclinical Solid Tumor Models 1306

M. Mata, C. Gerken, P. Nguyen, G. Krenciute, D.M. Spencer, and S. Gottschalk

Précis: Expression of an inducible MyD88/CD40 costimulatory molecule enhanced CAR T-cell efficacy, increasing tumor cell killing *in vivo* and suggesting the potential for improved activity against solid tumors.



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Notch Shapes the Innate Immunophenotype in Breast Cancer 1320

Q. Shen, B. Cohen, W. Zheng, R. Rahbar, B. Martin, K. Murakami, S. Lamorte, P. Thompson, H. Berman, J.C. Zúñiga-Pflücker, P.S. Ohashi, and M. Reedijk

Précis: NOTCH-recruited tumor-associated macrophages induce Notch-mediated IL1 β , CCL2, and TGF β paracrine signaling to promote a protumorigenic tumor microenvironment in breast cancer.

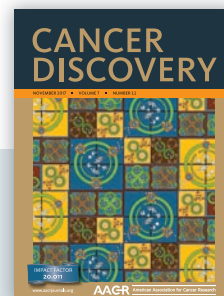
TOX Regulates Growth, DNA Repair, and Genomic Instability in T-cell Acute Lymphoblastic Leukemia 1336

R. Lobbardi, J. Pinder, B. Martinez-Pastor, M. Theodorou, J.S. Blackburn, B.J. Abraham, Y. Namiki, M. Mansour, N.S. Abdelfattah, A. Molodtsov, G. Alexe, D. Toiber, M. de Waard, E. Jain, M. Boukhali, M. Lion, D. Bhere, K. Shah, A. Gutierrez, K. Stegmaier, L.B. Silverman, R.I. Sadreyev, J.M. Asara, M.A. Oettinger, W. Haas, A.T. Look, R.A. Young, R. Mostoslavsky, G. Dellaire, and D.M. Langenau

Précis: A transgenic zebrafish screen identified TOX as an oncogenic driver in T-ALL, and TOX was shown to inhibit recruitment of KU70/KU80 to DNA repair sites to suppress NHEJ and promote genomic instability.

ON THE COVER

A screen of dimeric compounds based on antimalarial heterocycles identified the anticancer compound DQ661, which concurrently inhibited lysosomal catabolism and mTORC1 signaling. DQ661 bound to the lysosomal enzyme palmitoyl-protein thioesterase 1 (PPT1), which promotes proteolysis of palmitoylated proteins, and PPT1 inhibition phenocopied DQ661 treatment, resulting in palmitoylated protein accumulation and reduced mTORC1 signaling and lysosomal catabolism. *In vivo*, DQ661 could be combined with chemotherapy, and it suppressed the growth of melanoma xenografts and mouse colon and pancreatic tumors. The identification of DQ661 demonstrates that inhibitors concurrently targeting both mTORC1 signaling and lysosomal catabolism can suppress tumor growth. For details, please see the article by Rebecca, Nicastrì, McLaughlin, and colleagues on page 1266.



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Cancer Discov 2017;7:OF16-1353.

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