

# CANCER DISCOVERY CONTENTS

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**RESEARCH BRIEF** Opposing Effects of Androgen Deprivation and Targeted Therapy on Prostate Cancer Prevention ..... 44

S. Jia, X. Gao, S.H. Lee, S.-M. Maira, X. Wu, E.C. Stack, S. Signoretti, M. Loda, J.J. Zhao, and T.M. Roberts

**Précis:** Antiandrogen therapies promote prostate cancer progression, whereas blockade of PI3K and MAPK signaling suppresses tumor growth in the context of PTEN deficiency.

**RESEARCH ARTICLES** Genotype-Selective Combination Therapies for Melanoma Identified by High-Throughput Drug Screening ..... 52

M.A. Held, C.G. Langdon, J.T. Platt, T. Graham-Steed, Z. Liu, A. Chakraborty, A. Bacchiocchi, A. Koo, J.W. Haskins, M.W. Bosenberg, and D.F. Stern

See commentary, p. 14

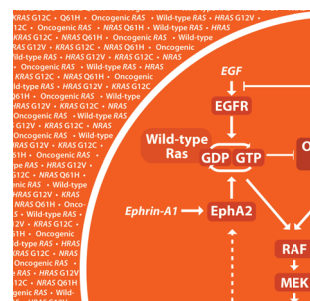
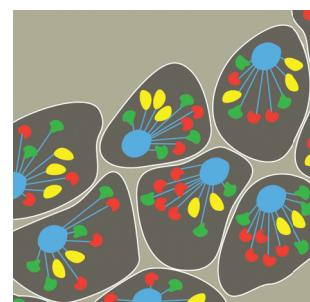
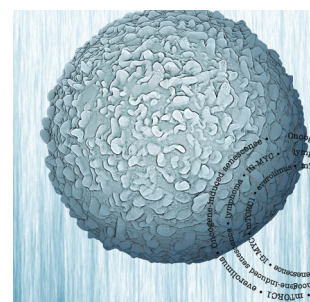
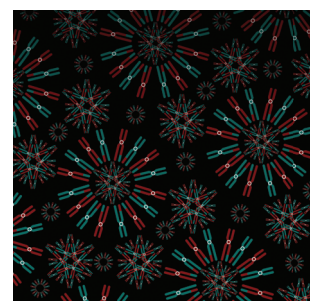
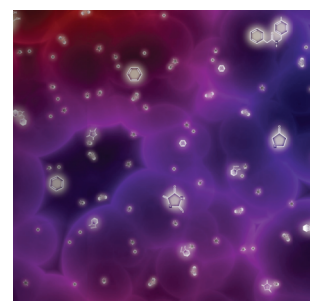
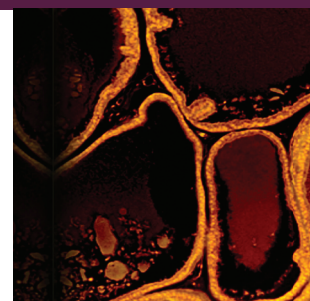
**Précis:** A systematic screening approach was used to characterize inhibitor combinations that are effective in melanomas driven by specific oncogenic mutations.

Loss of 53BP1 Causes PARP Inhibitor Resistance in *Brca1*-Mutated Mouse Mammary Tumors ..... 68

J.E. Jaspers, A. Kersbergen, U. Boon, W. Sol, L. van Deemter, S.A. Zander, R. Drost, E. Wientjens, J. Ji, A. Aly, J.H. Doroshov, A. Cranston, N.M.B. Martin, A. Lau, M.J. O'Connor, S. Ganesan, P. Borst, J. Jonkers, and S. Rottenberg

See commentary, p. 20

**Précis:** PARP inhibitor resistance can arise *in vivo* through partial restoration of homologous recombination caused by 53BP1 inactivation.



## The mTORC1 Inhibitor Everolimus Prevents and Treats Eμ-Myc Lymphoma by Restoring Oncogene-Induced Senescence.....82

M. Wall, G. Poortinga, K.L. Stanley, R.K. Lindemann, M. Bots, C.J. Chan, M.J. Bywater, K.M. Kinross, M.V. Astle, K. Waldeck, K.M. Hannan, J. Shortt, M.J. Smyth, S.W. Lowe, R.D. Hannan, R.B. Pearson, R.W. Johnstone, and G.A. McArthur

**Précis:** mTORC1-dependent bypass of MYC-induced senescence is required for the initiation and maintenance of Eμ-Myc B-cell lymphoma.

## Targeting C4-Demethylating Genes in the Cholesterol Pathway Sensitizes Cancer Cells to EGF Receptor Inhibitors via Increased EGF Receptor Degradation ... 96

A. Sukhanova, A. Gorin, I.G. Serebriiskii, L. Gabitova, H. Zheng, D. Restifo, B.L. Egleston, D. Cunningham, T. Bagnyukova, H. Liu, A. Nikonova, G.P. Adams, Y. Zhou, D.-H. Yang, R. Mehra, B. Burtneess, K.Q. Cai, A. Klein-Szanto, L.E. Kratz, R.I. Kelley, L.M. Weiner, G.E. Herman, E.A. Golemis, and I. Astsaturov

**Précis:** Sterol biosynthesis genes regulate EGFR endocytosis and signaling, and inhibition of these genes increases the efficacy of anti-EGFR therapies.

## Oncogenic and Wild-type Ras Play Divergent Roles in the Regulation of Mitogen-Activated Protein Kinase Signaling..... 112

A. Young, D. Lou, and F. McCormick

See commentary, p.24

**Précis:** Wild-type RAS isoforms regulate growth factor signaling in the context of oncogenic RAS and are required for optimal growth of cells harboring RAS mutations.

## Correction

## IDO Is a Nodal Pathogenic Driver of Lung Cancer and Metastasis Development ..... 124

For more News and Research Watch, visit *Cancer Discovery* online at <http://CDnews.aacrjournals.org>. Online-only News stories include the following:

- New ADC Effective against Prostate Cancer
- Proposals Aim to Make Trials More Efficient
- Triple Jeopardy for Triple-Negative Breast Cancers
- Sandy Underlines Need for Disaster Preparation
- Inhibiting JAK2 for Inflammatory Breast Cancer
- Bevacizumab Fails to Up Breast Cancer Survival

## ON THE COVER

Young and colleagues show that oncogenic and wild-type RAS isoforms have nonredundant, independent roles in cancer cells. Oncogenic RAS isoforms desensitize cells to receptor tyrosine kinase (RTK) stimulation and promote basal mitogen-activated protein kinase (MAPK) signaling, whereas wild-type RAS isoforms are required for RTK-dependent activation of MAPK signaling and optimal growth of cancer cells expressing oncogenic RAS. Depletion of oncogenic RAS sensitizes cells to wild-type isoform-mediated growth factor signaling, uncovering a potential resistance mechanism employed by RAS-mutant cells. Combined inhibition of RAS and RTK signaling effectively blocks growth of cells expressing oncogenic RAS and may therefore be a potential approach to circumvent resistance. For details, please see the article by Young and colleagues on page 112.

