

CANCER DISCOVERY CONTENTS

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ONLINE For more News and Research Watch, visit *Cancer Discovery* online at <http://CDnews.aacrjournals.org>.

VIEWS In The Spotlight

Shades of T790M: Intratumor Heterogeneity in EGFR-Mutant Lung Cancer 694

E. Ichihara and C.M. Lovly

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INPP4B Is a Tumor Suppressor in the Context of PTEN Deficiency 697

T.-T.T. Vo and D.A. Fruman

See article, p. 730

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Targeting MYC Translation in Colorectal Cancer 701

A. Castell and L.-G. Larsson

See article, p. 768

REVIEW APOBEC Enzymes: Mutagenic Fuel for Cancer Evolution and Heterogeneity 704

C. Swanton, N. McGranahan, G.J. Starrett, and R.S. Harris

RESEARCH BRIEFS

Heterogeneity Underlies the Emergence of EGFR^{T790} Wild-Type Clones Following Treatment of T790M-Positive Cancers with a Third-Generation EGFR Inhibitor 713



Z. Piotrowska, M.J. Niederst, C.A. Karlovich, H.A. Wakelee, J.W. Neal, M. Mino-Kenudson, L. Fulton, A.N. Hata, E.L. Lockerman, A. Kalsy, S. Digumarthy, A. Muzikansky, M. Raponi, A.R. Garcia, H.E. Mulvey, M.K. Parks, R.H. DiCecca, D. Dias-Santagata, A.J. Iafrate, A.T. Shaw, A.R. Allen, J.A. Engelman, and L.V. Sequist

Précis: Baseline intratumor heterogeneity for the EGFR^{T790M} mutation is associated with outgrowth of resistant EGFR^{T790M}-wild-type subclones and predicts clinical response to the EGFR^{T790M}-specific inhibitor rociletinib.

See commentary, p. 694

Germline Mutations in the CDKN2B Tumor Suppressor Gene Predispose to Renal Cell Carcinoma 723

M. Jafri, N.C. Wake, D.B. Ascher, D.E.V. Pires, D. Gentile, M.R. Morris, E. Rattenberry, M.A. Simpson, R.C. Trembath, A. Weber, E.R. Woodward, A. Donaldson, T.L. Blundell, F. Latif, and E.R. Maher

Précis: Germline inactivating mutations in CDKN2B were identified in patients with inherited renal cell carcinoma and predicted to impair its tumor suppressive activity.

INPP4B Is a PtdIns(3,4,5)P₃ Phosphatase That Can Act as a Tumor Suppressor 730

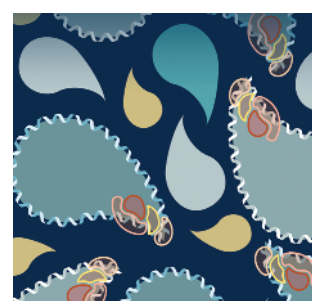
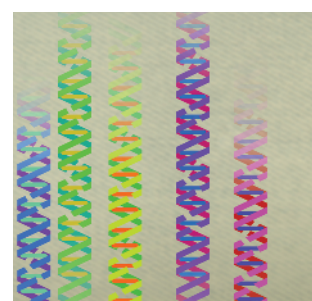
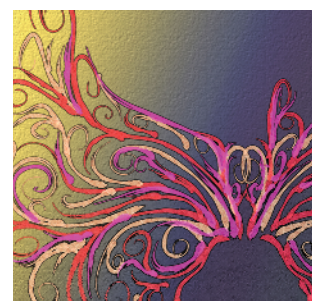
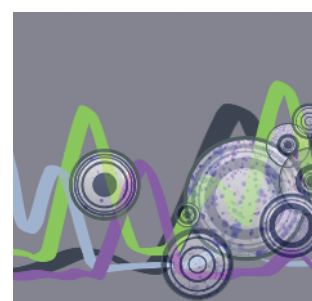
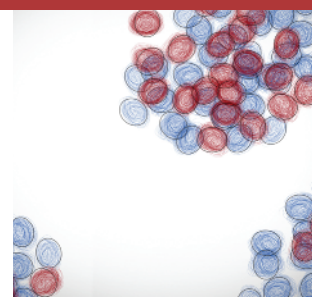


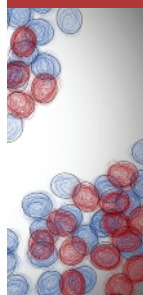
S. Kofuji, H. Kimura, H. Nakanishi, H. Nanjo, S. Takasuga, H. Liu, S. Eguchi, R. Nakamura, R. Itoh, N. Ueno, K. Asanuma, M. Huang, A. Koizumi, T. Habuchi, M. Yamazaki, A. Suzuki, J. Sasaki, and T. Sasaki

Précis: Loss of INPP4B in mice promotes enhanced AKT2 activation and PI(3,4,5)P₃ accumulation to induce metastatic thyroid tumors in the context of PTEN deficiency.

See commentary, p. 697

See article, p. 740





RESEARCH ARTICLES

In Vivo Role of INPP4B in Tumor and Metastasis Suppression through Regulation of PI3K-AKT Signaling at Endosomes 740

C.L. Chew, A. Lunardi, F. Gulluni, D.T. Ruan, M. Chen, L. Salmena, M. Nishino, A. Papa, C. Ng, J. Fung, J.G. Clohessy, J. Sasaki, T. Sasaki, R.T. Bronson, E. Hirsch, and P.P. Pandolfi

Précis: Loss of INPP4B drives localized activation of PI3K-AKT2 in early endosomes and cooperates with PTEN inactivation to promote aggressive and metastatic thyroid tumor formation.

See commentary, p. 697

See article, p. 730

ARID1A Deficiency Impairs the DNA Damage Checkpoint and Sensitizes Cells to PARP Inhibitors 752

J. Shen, Y. Peng, L. Wei, W. Zhang, L. Yang, L. Lan, P. Kapoor, Z. Ju, Q. Mo, I.-M. Shih, I.P. Uray, X. Wu, P.H. Brown, X. Shen, G.B. Mills, and G. Peng

Précis: The identification of a role of ARID1A in the DNA damage response suggests a potential therapeutic vulnerability of *ARID1A*-mutant cancers.

 AC icon indicates Author Choice

For more information please visit <http://www.aacrjournals.org>

Targeting Translation Initiation Bypasses Signaling Crosstalk Mechanisms That Maintain High MYC Levels in Colorectal Cancer 768

A. Wiegering, F.W. Uthe, T. Jamieson, Y. Ruoss, M. Hüttenrauch, M. Küspert, C. Pfann, C. Nixon, S. Herold, S. Walz, L. Taranets, C.-T. Germer, A. Rosenwald, O.J. Sansom, and M. Eilers

Précis: Silvestrol, an eIF4A inhibitor, circumvents feedback mechanisms that maintain MYC translation downstream of dual PI3K/mTOR inhibition to reduce MYC expression and inhibit colorectal cancer growth.

See commentary, p. 701

ON THE COVER

Shen and colleagues identified ARID1A, a subunit of SWI/SNF chromatin remodeling complexes, as a binding partner of ATR, a key regulator of the DNA damage response. ARID1A is recruited to DNA double-strand breaks (DSB) in an ATR-dependent manner and promotes efficient DSB end resection, which is necessary for activation of ATR and subsequent initiation and maintenance of the G₂/M checkpoint. ARID1A loss impaired homologous recombination and single-strand annealing DSB repair mechanisms and, similar to loss of BRCA1 or BRCA2, conferred sensitivity to DSB-inducing PARP inhibitors. Given that inactivating mutations in *ARID1A* are among the most frequent genetic events in human cancers, these findings suggest that PARP inhibitors may be effective in a broader spectrum of cancers than previously appreciated. For details, please see the article by Shen and colleagues on page 752.

