# **CANCER DISCOVERY**

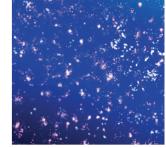
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TRKing Down an Old Oncogene in a New Era of Targeted Therapy ......25 A. Vaishnavi, A.T. Le, and R.C. Doebele



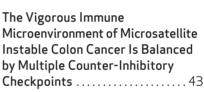
#### RESEARCH **BRIEFS**

Real-Time Intravital Imaging Establishes Tumor-Associated Macrophages as the Extraskeletal Target of Bisphosphonate 

S. Junankar, G. Shay, J. Jurczyluk, N. Ali, J. Down, N. Pocock, A. Parker, A. Nguyen, S. Sun, B. Kashemirov, C.E. McKenna, P.I. Croucher, A. Swarbrick, K. Weilbaecher, T.G. Phan, and M.J. Rogers

Précis: Bisphosphonates bind granular microcalcifications and are internalized by tumorassociated macrophages in breast tumors.

See commentary, p. 14

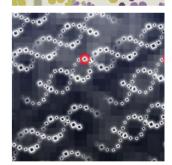


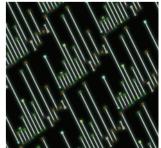
N.J. Llosa, M. Cruise, A. Tam, E.C. Wicks, E.M. Hechenbleikner, J.M. Taube, R.L. Blosser, H. Fan, H. Wang, B.S. Luber, M. Zhang, N. Papadopoulos, K.W. Kinzler, B. Vogelstein, C.L. Sears, R.A. Anders, D.M. Pardoll, and F. Housseau

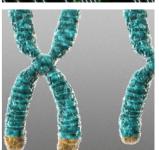
Précis: Mismatch repair-deficient colorectal cancers counteract Th1/CTL immune responses by upregulating immune checkpoint proteins, including PD-1 and PD-L1.

See commentary, p. 16









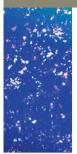
Mutant KRAS-Induced Expression of ICAM-1 in Pancreatic Acinar Cells Causes Attraction of Macrophages to Expedite the Formation of Precancerous Lesions ........... 52

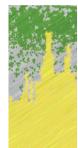


G.-Y. Liou, H. Döppler, B. Necela, B. Edenfield, L. Zhang, D.W. Dawson, and P. Storz

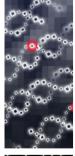
**Précis:** Crosstalk between pancreatic acinar cells and proinflammatory macrophages promotes initiation of acinar-to-ductal metaplasia via  $\mathsf{KRAS}^{\mathsf{G12D}}\text{-}\mathsf{induced}\,\mathsf{expression}\,\mathsf{of}\,\mathsf{the}$ macrophage chemoattractant ICAM1.

C.L. Chaffer and R.A. Weinberg













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D.M. Hyman, E.L. Diamond, C.R.T. Vibat, L. Hassaine, J.C. Poole, M. Patel, V.R. Holley, G. Cabrilo, T.T. Lu, M.E. Arcila, Y.R. Chung, R. Rampal, M.E. Lacouture, N. Rosen, F. Meric-Bernstam, J. Baselga, R. Kurzrock, M.G. Erlander, F. Janku, and O. Abdel-Wahab

**Précis:** Cell-free DNA testing using plasma and urine samples may be a reliable, noninvasive method to identify mutations and monitor treatment response in histiocytic disorders.

## RESEARCH ARTICLES

Measuring Residual Estrogen Receptor Availability during Fulvestrant Therapy in Patients with Metastatic Breast Cancer...72

M. van Kruchten, E.G. de Vries, A.W. Glaudemans, M.C. van Lanschot, M. van Faassen, I.P. Kema, M. Brown, C.P. Schröder, E.F. de Vries, and G.A. Hospers

**Précis:** Decreased [<sup>18</sup>F]fluoroestradiol uptake visualized by PET/CT provides a measure of tumor ER availability and correlates with fulvestrant treatment outcome in patients with metastatic breast cancer.

AC icon indicates Author Choice

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#### Induction of Telomere Dysfunction Mediated by the Telomerase Substrate Precursor 6-Thio-2'-Deoxyguanosine.... 82



I. Mender, S. Gryaznov, Z.G. Dikmen, W.E. Wright, and J.W. Shay

**Précis:** 6-thio-2'-deoxyguanosine is a precursor of a telomerase substrate that is incorporated into newly synthesized telomeres, leading to telomere dysfunction and death in telomerase-expressing

See commentary, p. 19

## ON THE COVER

Hyman, Diamond, and colleagues carried out a prospective, blinded study to quantitatively detect the *BRAF*<sup>V600E</sup> mutation in circulating tumor cellfree DNA (cfDNA) from the urine and plasma of patients with Langerhans cell histiocytosis or Erdheim-Chester disease. Urinary cfDNA analysis defined the *BRAF* genotype of all 30 patients and was 100% concordant with tissue genotypes among treatment-naïve patients. Furthermore, serial urinary cfDNA analyses in patients treated with a BRAF inhibitor or immunomodulatory therapy showed a progressive decrease in *BRAF*<sup>V600E</sup> allele burden, consistent with radiographic evidence of disease improvement. Tissue and cfDNA genotyping also identified a previously unreported somatic *KRAS*<sup>G125</sup> mutation in a *BRAF* wild-type patient. These data suggest cfDNA testing as a reliable, noninvasive method to detect *BRAF*<sup>V600E</sup> mutations and monitor response to therapy in histiocytic disorders. For details, please see the article by Hyman, Diamond, and colleagues on page 64.

