## IN THIS ISSUE
Highlighted research articles .................................. 681

## NEWS IN BRIEF
Important news stories affecting the community ............ 684

## NEWS IN DEPTH
PD-1 Blockade in GBM: Uncovering Response Clues ....... 687

## RESEARCH WATCH
Selected highlights of recent articles of exceptional significance from the cancer literature .................. 689

## ONLINE
For more News and Research Watch, visit Cancer Discovery online at http://cancerdiscovery.aacrjournals.org/CDNews.

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## VIEWS
In The Spotlight
Back to the Future: Rethinking and Rethinking IL2 in the Immune Checkpoint Inhibitor Era ............ 694
R.J. Sullivan
See article, p. 711

RAS Mutations Are Not Created Equal ...................... 696
G.A. Hobbs and C.J. Der
See article, p. 738

Kinase Networks Regulate Metabolism: I’D(H1) Never Have Guessed! ................................. 699
S. Horton and B.J.P. Huntly
See article, p. 756

## MINI REVIEW
Tumor Neurobiology and the War of Nerves in Cancer .... 702
S. Faulkner, P. Jobling, B. March, C.C. Jiang, and H. Hondermarck

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## RESEARCH BRIEF
A First-in-Human Study and Biomarker Analysis of NKTR-214, A Novel IL2Rβγ-Biased Cytokine, in Patients with Advanced or Metastatic Solid Tumors ........ 711
Précis: NKTR-214, a human recombinant IL2 attached to releasable polyethylene glycol chains to bias against binding to the low-affinity IL2Rα chain, promotes disease stabilization and stimulates immune cell infiltration in solid tumors.
See commentary, p. 694

## RESEARCH ARTICLES
PARP Inhibitor Efficacy Depends on CDB8 T-cell Recruitment via Intratumoral STING Pathway Activation in BRCA-Deficient Models of Triple-Negative Breast Cancer ...................... 722
Précis: PARP inhibition in BRCA-deficient TNBC tumors activates the cytosolic DNA-sensing cGAS/STING pathway to induce recruitment of CDB8 T cells to the tumor microenvironment.

Tissue-Specific Oncogenic Activity of KRAS146T .............. 738
Précis: Structural biology, mass spectrometry, and mouse modeling demonstrate the variable strength and tissue-specific effects of KRAS mutants in promoting cancer.
See commentary, p. 696
Mutant and Wild-Type Isocitrate Dehydrogenase 1 Share Enhancing Mechanisms Involving Distinct Tyrosine Kinase Cascades in Cancer .......... 756

Précis: Two distinct oncogenic tyrosine kinase cascades promote the activation of wild-type and mutant IDH1 in diverse cancers through direct and indirect phosphorylation of the Y42 and Y341 residues.
See commentary, p. 699

Cytokine-Regulated Phosphorylation and Activation of TET2 by JAK2 in Hematopoiesis ................. 778

Précis: JAK2-mediated phosphorylation and activation of TET2 increases TET2 DNA hydroxymethylation activity during hematopoietic differentiation and in myeloproliferative disease.

A Recurrent Activating Missense Mutation in Waldenström Macroglobulinemia Affects the DNA Binding of the ETS Transcription Factor SPI1 and Enhances Proliferation ...... 796

Précis: A mutation of SPI1 that is recurrent in Waldenström macroglobulinemia alters the DNA binding properties of SPI1 to activate genes typically regulated by other ETS transcription factors and confer a growth advantage.

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ON THE COVER Bentebibel, Hurwitz, Bernatchez, and colleagues report a first-in-human phase I study to evaluate the safety and activity of NKTR-214 (bempegaldesleukin), a human recombinant IL2 conjugated to slowly releasable polyethylene glycol chains that bias binding to the intermediate-affinity IL2Rβγ complex instead of the low-affinity IL2Rα chain. In heavily pretreated patients with advanced solid tumors, NKTR-214 was well tolerated, and the best overall response was stable disease in 14 of 26 evaluable patients (54%). NKTR-214 treatment induced activation and proliferation of immune cells in peripheral blood, and comparison of baseline and on-treatment tumor biopsies revealed that NKTR-214 increased T-cell activation signatures, CD8+ T-cell infiltration, and T-cell clonality. These findings suggest that NKTR-214 not only has immunostimulatory activity but may be a safer alternative to high-dose unconjugated IL2, making it an attractive candidate for combination immunotherapy strategies. For details, please see the article by Bentebibel, Hurwitz, Bernatchez, and colleagues on page 711.