## **CANCER** DISCOVERY

## CONTENTS

APRIL 2016 - VOLUME 6 - NUMBER 4

IN THIS ISSUE	Highlighted research articles
NEWS IN BRIEF	Important news stories affecting the community334
NEWS IN DEPTH	Boosting the Potency of T-cell Therapies338
RESEARCH WATCH	Selected highlights of recent articles of exceptional significance from the cancer literature
ONLINE	For more News and Research Watch, visit Cancer Discovery online at http://cancerdiscovery.aacrjournals.org/content/early/by/section.
VIEWS	In The Spotlight
	Molecular Mechanism of Mutant CALR-Mediated Transformation
	See article, p. 368
	STAT5 Loss Awakens the Dark Force in Natural Killer Cells347  J. Ni and A. Cerwenka  See article, p. 414
	Lifting Up the HAT: Synthetic Lethal Screening Reveals a Novel Vulnerability at the CBP-p300 Axis
REVIEW	Targeting CDK4 and CDK6:

### ARTICLES

**RESEARCH** Mutant Calreticulin Requires Both Its Mutant C-terminus and the Thrombopoietin Receptor for Oncogenic Transformation .....368



S. Elf, N.S. Abdelfattah, E. Chen, J. Perales-Patón, E.A. Rosen, A. Ko, F. Peisker, N. Florescu, S. Giannini, O. Wolach, E.A. Morgan, Z. Tothova, J.-A. Losman, R.K. Schneider, F. Al-Shahrour, and A. Mullally

> Précis: Mutant CALR alone is sufficient to induce myeloproliferative neoplasia and requires the mutant CALR C-terminus to transform cells via a thrombopoietin receptor-dependent activation of JAK-STAT signaling.

See commentary, p. 344

Reduced Proteolytic Shedding of Receptor Tyrosine Kinases Is a Post-Translational Mechanism of Kinase Inhibitor Resistance ....382



M.A. Miller, M.J. Oudin, R.J. Sullivan, S.J. Wang, A.S. Meyer, H. Im, D.T. Frederick, J. Tadros, L.G. Griffith, H. Lee, R. Weissleder, K.T. Flaherty, F.B. Gertler, and D.A. Lauffenburger

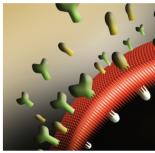
Précis: Kinase inhibitors reduce proteolytic shedding of surface receptors to enhance bypass signaling-induced resistance.

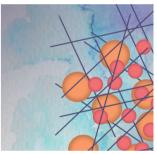
IFNy and CCL2 Cooperate to Redirect Tumor-Infiltrating Monocytes to Degrade Fibrosis and Enhance Chemotherapy Efficacy in Pancreatic Carcinoma .......400

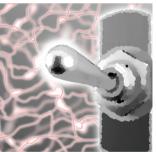
K.B. Long, W.L. Gladney, G.M. Tooker, K. Graham, J.A. Fraietta, and G.L. Beatty

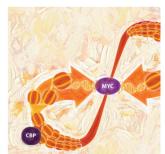
Précis: Activation of monocyte/ macrophage-dependent antifibrotic activity can potentiate gemcitabine efficacy in PDAC, and tumor fibrosis is a bidirectional process that can be reversed by regulating tumor-infiltrating monocytes.





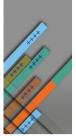






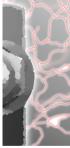


From Discovery to Therapy . . . . 353 C.J. Sherr, D. Beach, and G.I. Shapiro













# STAT5 Is a Key Regulator in NK Cells and Acts as a Molecular Switch from Tumor Surveillance to Tumor Promotion..... 414

D. Gotthardt, E.M. Putz, E. Grundschober, M. Prchal-Murphy, E. Straka, P. Kudweis, G. Heller, Z. Bago-Horvath, A. Witalisz-Siepracka, A.A. Cumaraswamy, P.T. Gunning, B. Strobl, M. Müller, R. Moriggl, C. Stockmann, and V. Sexl

**Précis:** In the absence of STAT5, NK cells secrete elevated levels of the angiogenic factor VEGFA, enhancing angiogenesis and promoting tumor formation.

See commentary, p. 347

Targeting p300 Addiction in CBP-Deficient Cancers Causes Synthetic Lethality by Apoptotic Cell Death due to Abrogation of MYC Expression...... 430

H. Ogiwara, M. Sasaki, T. Mitachi, T. Oike, S. Higuchi, Y. Tominaga, and T. Kohno

**Précis:** CBP and p300 exhibit synthetic lethality, whereby the loss or inhibition of the CBP paralog p300 in CBP-deficient cancers leads to cell death via downregulation of MYC.

See commentary, p. 350

AC icon indicates Author Choice

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

#### 

S.J. Blake, K. Stannard, J. Liu, S. Allen, M.C.R. Yong, D. Mittal, A.R. Aguilera, J.J. Miles, V.P. Lutzky, L. Ferrari de Andrade, L. Martinet, M. Colonna, K. Takeda, F. Kühnel, E. Gurlevik, G. Bernhardt, M.W.L. Teng, and M.J. Smyth

**Précis:** Monoclonal antibodies against CD96 inhibit metastasis by enhancing cytotoxic NK cell activity and may be used in combination with other immunotherapeutic and chemotherapeutic agents.



## ON THE COVER

Miller, Oudin, and colleagues showed that treatment with MEK inhibitors resulted in reduced levels of circulating receptor tyrosine kinases (RTK), increased tumor expression of RTKs, and decreased metalloproteinase activity. Circulating RTK levels were correlated with progression-free survival in patients with melanoma and kinase inhibitor resistance. MEK inhibitor treatment promoted the association of tissue inhibitor of metalloproteinase 1 (TIMP1) with metalloproteinases to induce the accumulation of AXL on the cell surface and subsequently drive the activation of JNK bypass signaling. These findings identify a bypass mechanism by which kinase inhibitors reduce proteolytic shedding of surface receptors and show that kinase inhibitor resistance may be overcome by neutralizing TIMP1 or the addition of a bypass RTK inhibitor. For details, please see the article by Miller, Oudin, and colleagues on page 382.