IN THIS ISSUE
Highlighted research articles

NEWS IN BRIEF
Important news stories affecting the community

NEWS IN DEPTH
Q&A: Mitchell Zeller on the FDA and Tobacco
The Science of Tobacco Addiction and Cessation

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://CDnews.aacrjournals.org.

REVIEW
Antiangiogenic Therapies: Going beyond Their Limits
L. Moserle, G. Jiménez-Valerio, and O. Casanovas

RESEARCH BRIEFS
mTOR Inhibition Specifically Sensitizes Colorectal Cancers with KRAS or BRAF Mutations to BCL-2/BCL-XL Inhibition by Suppressing MCL-1
Précis: mTORC inhibitors decrease MCL-1 translation and cooperate with BCL-2/BCL-XL inhibitors to induce apoptosis and growth arrest in KRAS- and BRAF-mutant colorectal cancer.
See commentary, p. 19

Restricted Expression of miR-30c-2-3p and miR-30a-3p in Clear Cell Renal Cell Carcinomas Enhances HIF2α Activity
Précis: Repression of specific miRNAs antagonizes the tumor-suppressive activity of HIF1α in ccRCC tumors by augmenting expression of the oncoprotein HIF2α.
See commentary, p. 22

MAP Kinase Pathway Alterations in BRAF-Mutant Melanoma Patients with Acquired Resistance to Combined RAF/MEK Inhibition
Précis: Whole-exome and transcriptome sequencing of dabrafenib- and trametinib-resistant melanomas identifies putative mechanisms of acquired resistance to combined RAF/MEK inhibition.
See commentary, p. 27

CANCER DISCOVERY JANUARY 2014
www.aacrjournals.org
Using data from a high-throughput drug screen, Faber and colleagues found that AZD8055, an inhibitor of mTOR complexes 1 and 2 (TORC1/2), cooperated with the BCL-2/BCL-XL inhibitor ABT-263 to induce cell-cycle arrest and apoptosis specifically in 

KRAS- and 

BRAF-mutant colorectal cancer cell lines. This genotype selectivity was mediated by suppression of the antiapoptotic protein MCL-1 and disruption of BIM–MCL-1 complexes in response to TORC1/2 inhibition, which sensitized KRAS-mutant cells to ABT-263 and triggered apoptosis. Furthermore, dual treatment with ABT-263 and AZD8055 preferentially induced tumor regression in KRAS-mutant colorectal cancer xenograft and genetically engineered mouse models. These results support further clinical development of this therapeutic combination for patients with KRAS- and BRAF-mutant colorectal cancer. For details, please see the article by Faber and colleagues on page 42.

**ON THE COVER**

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**RESEARCH ARTICLES**

**A Novel AKT1 Mutant Amplifies an Adaptive Melanoma Response to BRAF Inhibition**


See commentary, p. 27

**Acquired Resistance and Clonal Evolution in Melanoma during BRAF Inhibitor Therapy**


Précis: Acquired BRAF inhibitor resistance is driven by heterogeneous genetic alterations that promote MAPK reactivation, PI3K-AKT upregulation, and branched clonal evolution.

See commentary, p. 27

**The Genetic Landscape of Clinical Resistance to RAF Inhibition in Metastatic Melanoma**


Précis: Whole-exome sequencing identifies diverse mechanisms of resistance to vemurafenib or dabrafenib, many of which result in MAPK pathway reactivation.

See commentary, p. 27

**Defective Stromal Remodeling and Neutrophil Extracellular Traps in Lymphoid Tissues Favor the Transition from Autoimmunity to Lymphoma**


Précis: Loss of the matricellular protein SPARC leads to altered stromal remodeling and abnormal neutrophil activity that exacerbate autoimmunity and promote B-cell transformation.

See commentary, p. 25

**The Genetic Landscape of Clinical Resistance to RAF Inhibition in Metastatic Melanoma**


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See commentary, p. 27