## CONTENTS

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#### VOLUME 4  
#### NUMBER 1

<table>
<thead>
<tr>
<th>IN THIS ISSUE</th>
<th>Highlighted research articles</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEWS IN BRIEF</td>
<td>Important news stories affecting the community</td>
<td>6</td>
</tr>
<tr>
<td>NEWS IN DEPTH</td>
<td>Q&amp;A: Mitchell Zeller on the FDA and Tobacco</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>The Science of Tobacco Addiction and Cessation</td>
<td>12</td>
</tr>
<tr>
<td>RESEARCH WATCH</td>
<td>Selected highlights of recent articles of exceptional significance from the cancer literature</td>
<td>14</td>
</tr>
<tr>
<td>ONLINE</td>
<td>For more News and Research Watch, visit Cancer Discovery online at <a href="http://CDnews.aacrjournals.org">http://CDnews.aacrjournals.org</a></td>
<td></td>
</tr>
</tbody>
</table>

#### REVIEW

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

**mTOR Inhibition Specifically Sensitizes Colorectal Cancers with KRA5 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

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**RESEARCH BRIEFS**

**Climbing RAS, the Everest of Oncogenes**  
M. Russo, F. Di Nicolantonio, and A. Bardelli  
*See article, p. 42*

**miR-30c-2-3p and miR-30a-3p: New Pieces of the Jigsaw Puzzle in HIF2α Regulation**  
H. Moch and M. Lukamowicz-Rajska  
*See article, p. 53*

**Faulty ECM Signaling Facilitates Autoimmune Lymphomagenesis**  
R.A. Brekken  
*See article, p. 110*

**Towards a Unified Model of RAF Inhibitor Resistance**  
D.B. Solit and N. Rosen  
*See articles, p. 61, p. 69, p. 80, p. 94*

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**IN THIS ISSUE**

**NEWS IN BRIEF**

**NEWS IN DEPTH**

**RESEARCH WATCH**

**ONLINE**

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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 \( \text{KRAS} \) - and \( \text{BRAF} \)-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 \( \text{KRAS} \)-mutant cells to ABT-263 and triggered apoptosis. Furthermore, dual treatment with ABT-263 and AZD8055 preferentially induced tumor regression in \( \text{KRAS} \)-mutant colorectal cancer xenograft and genetically engineered mouse models. These results support further clinical development of this therapeutic combination for patients with \( \text{KRAS} \)- and \( \text{BRAF} \)-mutant colorectal cancer.

For details, please see the article by Faber and colleagues on page 42.

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**RESEARCH ARTICLES**

**A Novel AKT1 Mutant Amplifies an Adaptive Melanoma Response to BRAF Inhibition** .............................. 69


*See commentary, p. 27*

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**Acquired Resistance and Clonal Evolution in Melanoma during BRAF Inhibitor Therapy** .............................. 80


*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*

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**The Genetic Landscape of Clinical Resistance to RAF Inhibition in Metastatic Melanoma** ............................. 94


*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*

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**Defective Stromal Remodeling and Neutrophil Extracellular Traps in Lymphoid Tissues Favor the Transition from Autoimmunity to Lymphoma** ............. 110


*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*

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