# TABLE OF CONTENTS

## BREAKING INSIGHTS

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1625</td>
<td>Highlights from Recent Cancer Literature</td>
<td></td>
</tr>
</tbody>
</table>

## REVIEW

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
</table>

## CANCER RESEARCH HIGHLIGHTS

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1633</td>
<td>Mdm2 and MdmX: Partners in p53 Destruction</td>
<td>James J. Manfredi</td>
</tr>
<tr>
<td>See related article by Yang et al., Cancer Res 2021;81:898–909</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1635</td>
<td>A Complementary Strategy to Mitigate Radiation-Induced Cognitive Decline</td>
<td>Navyateja Korimerla and Daniel R. Wahl</td>
</tr>
<tr>
<td>See related article, p. 1732</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1637</td>
<td>Beyond Stamp Collecting: Evolutionary and Functional Genomics Advance Our Understanding of Cancer Biology</td>
<td>Joseph Lachance</td>
</tr>
<tr>
<td>See related article, p. 1695</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## GENOME AND EPIGENOME

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
</table>

This study shows how HSF1 regulates a stromal transcriptional program associated with aggressive gastric cancer and identifies multiple proteins within this program as candidates for therapeutic intervention. |

Targeting TUG1 coupled with a cancer-specific drug delivery system effectively modulates S-FU catabolism in TUG1-overexpressing PDAC cells, thus contributing to a new combinatorial strategy for cancer treatment. |
A Large-Scale Association Study Detects Novel Rare Genetic Variants in the p53 Pathway to Affect Cancer Risk, Progression, and Drug Response
These results offer evidence of how cancer susceptibility SNPs can interact with cancer driver genes to affect cancer progression and present novel therapeutic targets.

Multimomics Characterization of Low-Grade Serous Ovarian Carcinoma Identifies Potential Biomarkers of MEK Inhibitor Sensitivity and Therapeutic Vulnerability
These findings highlight the utility of global multimomics to characterize LGSOC cell lines as research models, to determine biomarkers of MEK resistance, and to identify potential novel therapeutic targets.

A Large-Scale Association Study Detects Novel Rare Variants, Risk Genes, Functional Elements, and Polygenic Architecture of Prostate Cancer Susceptibility
This study maps the biological relationships between diverse risk factors for prostate cancer, integrating different functional datasets to interpret and model genome-wide data from over 200,000 men with and without prostate cancer.
See related commentary, p. 1637

MOLECULAR CELL BIOLOGY

CKAP2L Promotes Non-Small Cell Lung Cancer Progression through Regulation of Transcription Elongation
Tiziana Monteverde, Sudhakar Sahoo, Manuela La Montagna, Peter Magee, Lei Shi, Dave Lee, Robert Sellers, Alexander R. Baker, Hui Sun Leong, Matteo Fassan, and Michela Garofalo
These findings demonstrate the oncogenic function of CKAP2L through regulation of transcription elongation and suggest that targeting CKAP2L could enhance therapeutic response in patients with NSCLC.

ELOVL5 Is a Critical and Targetable Fatty Acid Elongase in Prostate Cancer
This study identifies phospholipid elongation as a novel metabolic target of androgen action that is critical for prostate tumor metastasis.

Glia-Selective Deletion of Complement C1q Prevents Radiation-Induced Cognitive Deficits and Neuroinflammation
Clinically-relevant radiotherapy induces aberrant complement activation, leading to brain injury. Microglia-selective genetic deletion of CNS complement C1q ameliorates radiation-induced cognitive impairments, synaptic loss, and neuroinflammation, highlighting the potential for C1q as a novel therapeutic target.
See related commentary, p. 1635

PINK1-Mediated Inhibition of EGFR Dimerization and Activation Impedes EGFR-Driven Lung Tumorigenesis
Emily Pei-Ying Lin, Bo-Tsang Huang, Wei-Yun Lai, Yi-Ting Tseng, Shuenn-Chen Yang, Hao-Cheng Kuo, and Pan-Chry Yang
This study identifies PINK1 as a critical tumor suppressor that impedes EGFR dimerization and highlights PINK1-CTD as a potential therapeutic agent in EGFR-driven lung cancer.
RINT1 Regulates SUMOylation and the DNA Damage Response to Preserve Cellular Homeostasis in Pancreatic Cancer
These findings provide new insights into the aggressive behavior of PDAC, showing that RINT1 directly correlates with survival in patients with PDAC by disturbing the SUMOylation process, a crucial modification in carcinogenesis.

Cooperative Targeting of Immunotherapy-Resistant Melanoma and Lung Cancer by an AXL-Targeting Antibody–Drug Conjugate and Immune Checkpoint Blockade
These findings show that targeting AXL-positive tumor fractions with an antibody–drug conjugate enhances antitumor immunity in several humanized tumor models of melanoma and lung cancer.

Serial Stimulation of Invariant Natural Killer T Cells with Covalently Stabilized Bispecific T-cell Engagers Generates Antitumor Immunity While Avoiding Anergy
These findings demonstrate that the single-cell regulatory heterogeneity of small-cell lung cancer becomes increasingly elaborate in the liver, a common metastatic site for the disease.

See related articles, p. 1840 and p. 1868
1868  Premalignant Oligodendrocyte Precursor Cells Stall in a Heterogeneous State of Replication Stress Prior to Gliomagenesis  
Matthew D. Sutcliffe, Rui P. Galvao, Lixin Wang, Jungeun Kim, Lauren K. Rosenfeld, Shambhavi Singh, Hui Zong, and Kevin A. Janes  
Profiling premalignant cell states in a mouse model of glioma uncovers regulatory heterogeneity in glioma cells-of-origin and defines a state of replication stress that precedes tumor initiation.  
See related articles, p. 1840 and p. 1853

1883  The Hydroxyquinoline Analogue YUM70 Inhibits GRP78 to Induce ER Stress–Mediated Apoptosis in Pancreatic Cancer  
Soma Samanta, Suhui Yang, Bikash Debnath, Ding Xue, Yuting Kuang, Kavya Ramkumar, Amy S. Lee, Mats Ljungman, and Nouri Neamati  
This study identifies a novel ER stress inducer that binds GRP78 and inhibits pancreatic cancer cell growth in vitro and in vivo, demonstrating its potential as a therapeutic agent for pancreatic cancer.

1896  MYCN-Amplified Neuroblastoma Is Addicted to Iron and Vulnerable to Inhibition of the System Xc-/Glutathione Axis  
The study shows how MYCN increases intracellular iron levels and subsequent GSH pathway activity and demonstrates the antitumor activity of FDA-approved SAS and auranofin in patient-derived xenograft models of MYCN-amplified neuroblastoma.

1909  Delta-Like Ligand–Notch1 Signaling Is Selectively Modulated by HPV16 E6 to Promote Squamous Cell Proliferation and Correlates with Cervical Cancer Prognosis  
This study investigates cervical cancer cell-of-origin populations and describes a DLL-Notch1 phenotype that is associated with disease prognosis and that might help identify cells that are susceptible to HPV-induced carcinogenesis.

1922  Local Targeting of NAD⁺ Salvage Pathway Alters the Immune Tumor Microenvironment and Enhances Checkpoint Immunotherapy in Glioblastoma  
Ming Li, Ameya R. Kirtane, Juri Kiyokawa, Hiroaki Nagashima, Aaron Lopes, Zain A. Tirmizi, Christine K. Lee, Giovanni Traverso, Daniel P. Cahill, and Hiroaki Wakimoto
Immunofluorescent staining of DLL4 in a keratinocyte cell line, NIKS, highlights the high expression of this Notch1 ligand in migratory and proliferative cells of the leading edge of large monolayer gaps. This DLL4 phenotype is inherent to reserve cells in the normal, HPV-uninfected cervix, and HPV16 E6 expression sustains Notch1 ligand expression, likely facilitating a more durable skewing of squamous cell fate. Cervical tumors that show high DLL4 expression are associated with worse disease prognosis. For details, see Khelil and colleagues on page 1909.