### BREAKING ADVANCES

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**Highlights from Recent Cancer Literature**

### REVIEWS

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**Long Noncoding RNA, Polycomb, and the Ghosts Haunting INK4b-ARF-INK4a Expression**
Francesca Aguilo, Ming-Ming Zhou, and Martin J. Walsh

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**B-Myb, Cancer, Senescence, and MicroRNAs**
Ivan Martinez and Daniel DiMaio

### PRIORITY REPORTS

5374

**Indirubins Decrease Glioma Invasion by Blocking Migratory Phenotypes in Both the Tumor and Stromal Endothelial Cell Compartments**
Shante P. Williams, Michal O. Nowicki, Fang Liu, Rachael Press, Jakub Godlewski, Mahmoud Abdel-Rasoul, Balveen Kaur, Soledad A. Fernandez, E. Antonio Chiocca, and Sean E. Lawler

**Précis:** Preclinical studies validate a novel class of small molecule inhibitors of the enzyme GSK-3, which exert potent antitumor properties by blocking both tumor invasion and angiogenesis.

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**Imatinib Sensitivity in BCR-ABL1–Positive Chronic Myeloid Leukemia Cells Is Regulated by the Remaining Normal ABL1 Allele**
Anna Virgili, Mateusz Koptyra, Yashodhara Dasgupta, Eliza Glodkowska-Mrowka, Tomasz Stoklosa, Elisabeth P. Nacheva, and Tomasz Skorski

**Précis:** The lack of a complete cytogenetic response in chronic phase CML patients treated with the ABL kinase inhibitor imatinib can be explained by loss of the remaining normal ABL1 allele in CML cells.

### INTEGRATED SYSTEMS AND TECHNOLOGIES

5400

**Comparing Signaling Networks between Normal and Transformed Hepatocytes Using Discrete Logical Models**

**Précis:** Findings illustrate a novel approach to creating cell-specific computational models of signaling networks based on biochemical data, applying it in this study to define deregulated pathways in hepatocellular carcinoma.
Profound Coordinated Alterations of Intratumoral NK Cell Phenotype and Function in Lung Carcinoma

Sophia Platonova, Julien Cherfils-Vicini, Diane Damotte, Lucile Crozet, Vincent Vieillard, Pierre Validire, Pascale André, Marie-Caroline Dieu-Nosjean, Marco Alfano, Jean-François Régnard, Wolf-Herman Fridman, Catherine Sautès-Fridman, and Isabelle Cremer

Precise: The tissue microenvironment in human lung carcinomas suppresses the tumoricidal activity of natural killer cells, thereby contributing to immune escape and progression.

Quantitative and Functional Alterations of Plasmacytoid Dendritic Cells Contribute to Immune Tolerance in Ovarian Cancer

Sana Intidhar Labidi-Galy, Vanja Sisirak, Pierre Meeus, Michael Gobert, Isabelle Treilleux, Agathe Bajard, Jean-Damien Combes, Alexandre Cassignon, Olivier Tredan, Isabelle Durand, Christine Ménétrier-Caux, Christophe Caux, Jean-Yves Blay, Isabelle Ray-Coquard, and Nathalie Bendriss-Vermare

Precise: Findings define a critical cellular mechanism of immune escape in human ovarian cancers, offering new insights into the pathophysiology of this often fatal cancer.

A Novel Tumor Antigen Derived from Enhanced Degradation of Bax Protein in Human Cancers

Claudia Trindade Nunes, Kelly L. Miners, Garry Dolton, Chris Pepper, Chris Fegan, Malcolm D. Mason, and Stephen Man

Precise: Study findings suggest that useful peptide antigens for cancer vaccination might be derived from proteins commonly expressed in normal cells but abnormally proteolyzed in cancer.

The ICOS/ICOSL Pathway Is Required for Optimal Antitumor Responses Mediated by Anti–CTLA-4 Therapy

Tihui Fu, Qiuming He, and Padmanee Sharma

Precise: Findings elucidate how antitumor responses are elicited by CTLA-4 antibody ipilimumab, recently approved by the FDA for treatment of melanoma.

Maximal T Cell–Mediated Antitumor Responses Rely upon CCR5 Expression in Both CD4+ and CD8+ T Cells

Alicia González-Martín, Lucio Gómez, Joseph Lastgarten, Emilia Mira, and Santos Mañes

Precise: A chemokine receptor that is critical to organize leukocyte trafficking responses to infection is also found to be critical for T cell-mediated responses against tumors, suggesting mechanistic similarities in the way that the immune system interprets cancer cells and infectious pathogens.

TLR4 Engagement during TLR3-Induced Proinflammatory Signaling in Dendritic Cells Promotes IL-10–Mediated Suppression of Antitumor Immunity

Dusan Bogunovic, Olivier Manches, Emmanuelle Godefroy, Alice Weydall, Anne Gallois, Andres M. Salazar, Isabelle Marie, David E. Levy, and Nina Bhardwaj

Precise: Findings suggest that the antitumor properties of a potent immune stimulatory Toll receptor ligand with therapeutic potential may be reduced or negated if the Toll receptor TLR4 is also activated, with implications for the design of immunotherapy trials.

Comparison of Increased Aromatase versus ERα in the Generation of Mammary Hyperplasia and Cancer

Edgar S. Díaz-Cruz, Yasuro Sugimoto, G. Ian Gallicano, Robert W. Brueggemeier, and Priscilla A. Furth

Precise: Findings show that increased aromatase levels may play an even larger role in breast cancer progression than overexpression of estrogen receptor α.

Ap16/AIM/Spa/CD5L Overexpression in Alveolar Type II Epithelial Cells Induces Spontaneous Lung Adenocarcinoma

Yuan Li, Peng Qu, Lingyan Wu, Beilin Li, Hong Du, and Cong Yan

Precise: This study illustrates the importance of "immunogenic" cell death signaling for blocking lung cancer, the progression of which relies upon the activation of proinflammatory mechanisms that not only block cancer cell apoptosis but also promote their immune escape.
VHL Gene Mutations and Their Effects on Hypoxia Inducible Factor HIFα: Identification of Potential Driver and Passenger Mutations
Markus P. Rechsteiner, Adriana von Teichman, Anna Nowicka, Tullio Sulser, Peter Schraml, and Holger Moch

Precise: Understanding the functional impact of specific mutations in the VHL tumor suppressor pathway in deadly kidney cancers may be critical for selecting appropriate individualized therapies in patients.

Increased VEGFR-2 Gene Copy Is Associated with Chemoresistance and Shorter Survival in Patients with Non–Small-Cell Lung Carcinoma Who Receive Adjuvant Chemotherapy

Precise: Results show an association between VEGFR-2 copy number gains and reduced overall survival in patients with non–small cell lung cancer.

CXCL12/CXCR4 Blockade Induces Multimodal Antitumor Effects That Prolong Survival in an Immunocompetent Mouse Model of Ovarian Cancer
Elda Righi, Satoshi Kashiwagi, Jianping Yuan, Michael Santosuosso, Pierre Leblanc, Rachel Ingraham, Benjamin Forbes, Beth Edelblute, Brian Collette, Deyin Xing, Magdalena Kowalski, Maria Cristina Mingari, Fabrizio Vianello, Michael Birrer, Sandra Orsulic, Glenn Dranoff, and Mark C. Poznansky

Precise: A druggable target implicated in promoting metastasis is found to coordinately promote immune escape, illustrating the important linkage between these two processes in ovarian cancer progression.

Identification of the MEK1(F129L) Activating Mutation as a Potential Mechanism of Acquired Resistance to MEK Inhibition in Human Cancers Carrying the B-Raf/V600E Mutation
Huisheng Wang, Sherif Daouti, Wen-hui Li, Yang Wen, Christine Rizzo, Brian Higgins, Kathryn Packman, Neal Rosen, John F. Boylan, David Heimbrook, and Hui Feng Niu

Precise: Combined inhibition of Raf and MEK may offer a clinical strategy to bypass or overcome acquired resistance to MEK inhibitors that can arise as the result of a powerful activating mutation in MEK1.

GPR56 Regulates VEGF Production and Angiogenesis during Melanoma Progression
Liquan Yang, Guangchun Chen, Sonali Mohanty, Glynis Scott, Fabeha Fazal, Arshad Rahman, Shahinoor Begum, Richard O. Hynes, and Lei Xu

Precise: Findings identify a novel G protein-coupled receptor that regulates VEGF production, offering a new therapeutic target for angiogenesis inhibition.

YB-1 Bridges Neural Stem Cells and Brain Tumor–Initiating Cells via Its Roles in Differentiation and Cell Growth

Precise: A transcription factor required for embryonic brain development also contributes in later life to brain tumor development, due to its roles in normal and malignant neural stem cells.
Protein Arginine Methyltransferase 5 Accelerates Tumor Growth by Arginine Methylation of the Tumor Suppressor Programmed Cell Death 4
Matthew A. Powers, Marta M. Fay, Rachel E. Factor, Alana L. Welm, and Katharine S. Ullman

Précis: This article reports a new regulatory node in cancer in which a protein methyltransferase works in conjunction with the tumor suppressor PDCD4 to cause accelerated tumor growth.

p53-Dependent Regulation of Mitochondrial Energy Production by the RelA Subunit of NF-κB
Renée F. Johnson, Ini-Isabée Witzel, and Neil D. Perkins

Précis: This study defines an important new link in the control of mitochondrial function by oncogenes that influence cellular metabolism.

ABOUT THE COVER
The Y-box binding protein (YB-1) is an oncogenic transcription factor known for its ability to cause drug resistance and cancer recurrence. Fotovati and colleagues report that YB-1 supports brain tumor–initiating cells by inhibiting differentiation through the maintenance of proteins associated with stem cells. In cancer-derived neurospheres grown from pediatric glioblastoma multiforme cells, YB-1 was highly expressed along with the stem cell markers nestin and Bmi-1. For details, see the article by Fotovati and colleagues on page 5569 of this issue.