

## BREAKING ADVANCES

- 5363 | **Highlights from Recent Cancer Literature**

## REVIEWS

- 5365 | **Long Noncoding RNA, Polycomb, and the Ghosts Haunting *INK4b-ARF-INK4a* Expression**  
 Francesca Aguilo, Ming-Ming Zhou, and Martin J. Walsh
- 5370 | **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**  
 Shanté 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.

- 5381 | **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.

- 5387 | **TMPRSS2-ERG-Mediated Feed-Forward Regulation of Wild-Type ERG in Human Prostate Cancers**  
 Ram-Shankar Mani, Matthew K. Iyer, Qi Cao, J. Chad Brenner, Lei Wang, Aparna Ghosh, Xuhong Cao, Robert J. Lonigro, Scott A. Tomlins, Sooryanarayana Varambally, and Arul M. Chinnaiyan

*Précis:* This study identifies an important mechanism of ERG regulation in human prostate cancers, with implications for understanding prostate tumor progression.

- 5393 | **IL-18 Induces PD-1-Dependent Immunosuppression in Cancer**  
 Magali Terme, Evelyn Ullrich, Laetitia Aymeric, Kathrin Meinhardt, Mélanie Desbois, Nicolas Delahaye, Sophie Viaud, Bernard Ryffel, Hideo Yagita, Gilles Kaplanski, Armelle Prévost-Blondel, Masashi Kato, Joachim L. Schultze, Eric Tartour, Guido Kroemer, Nathalie Chaput, and Laurence Zitvogel

*Précis:* IL-18 suppresses the crucial role of natural killer cells in supporting tumor immunosurveillance, with implications for clinical strategies to reverse this mechanism of tumoral immune escape.

## INTEGRATED SYSTEMS AND TECHNOLOGIES

- 5400 | **Comparing Signaling Networks between Normal and Transformed Hepatocytes Using Discrete Logical Models**  
 Julio Saez-Rodriguez, Leonidas G. Alexopoulos, MingSheng Zhang, Melody K. Morris, Douglas A. Lauffenburger, and Peter K. Sorger

*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.

## MICROENVIRONMENT AND IMMUNOLOGY

- 5412 **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 Alifano, Jean-François Régnard, Wolf-Herman Fridman, Catherine Sautès-Fridman, and Isabelle Cremer

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

- 5423 **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, Julien Faget, François Mithieux, Alexandre Cassagnol, Olivier Tredan, Isabelle Durand, Christine Ménétrier-Caux, Christophe Caux, Jean-Yves Blay, Isabelle Ray-Coquard, and Nathalie Bendriss-Vermare

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

- 5435 **A Novel Tumor Antigen Derived from Enhanced Degradation of Bax Protein in Human Cancers**  
Cláudia Trindade Nunes, Kelly L. Miners, Garry Dolton, Chris Pepper, Chris Fegan, Malcolm D. Mason, and Stephen Man

*Précis:* 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.

- 5445 **The ICOS/ICOSL Pathway Is Required for Optimal Antitumor Responses Mediated by Anti-CTLA-4 Therapy**  
Tihui Fu, Qiuming He, and Padmanee Sharma

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

- 5455 **Maximal T Cell–Mediated Antitumor Responses Rely upon CCR5 Expression in Both CD4<sup>+</sup> and CD8<sup>+</sup> T Cells**  
Alicia González-Martín, Lucio Gómez, Joseph Lustgarten, Emilia Mira, and Santos Mañes

*Précis:* 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.

- 5467 **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 Yewdall, Anne Gallois, Andres M. Salazar, Isabelle Marie, David E. Levy, and Nina Bhardwaj

*Précis:* 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.

## MOLECULAR AND CELLULAR PATHOBIOLOGY

- 5477 **Comparison of Increased Aromatase versus ER $\alpha$  in the Generation of Mammary Hyperplasia and Cancer**  
Edgar S. Díaz-Cruz, Yasuro Sugimoto, G. Ian Gallicano, Robert W. Brueggemeier, and Priscilla A. Furth

*Précis:* Findings show that increased aromatase levels may play an even larger role in breast cancer progression than overexpression of estrogen receptor  $\alpha$ .

- 5488 **Api6/AIM/Sp $\alpha$ /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

*Précis:* 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.

5500 **VHL Gene Mutations and Their Effects on Hypoxia Inducible Factor HIF $\alpha$ : Identification of Potential Driver and Passenger Mutations**

Markus P. Rechsteiner, Adriana von Teichman, Anna Nowicka, Tullio Sulser, Peter Schraml, and Holger Moch

*Précis:* 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.

5512 **Increased VEGFR-2 Gene Copy Is Associated with Chemoresistance and Shorter Survival in Patients with Non-Small-Cell Lung Carcinoma Who Receive Adjuvant Chemotherapy**

Fei Yang, Ximing Tang, Erick Riquelme, Carmen Behrens, Monique B. Nilsson, Uma Giri, Marileila Varella-Garcia, Lauren A. Byers, Heather Y. Lin, Jing Wang, Maria G. Raso, Luc Girard, Kevin Coombes, J. Jack Lee, Roy S. Herbst, John D. Minna, John V. Heymach, and Ignacio I. Wistuba

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

5535 **Identification of the MEK1(F129L) Activating Mutation as a Potential Mechanism of Acquired Resistance to MEK Inhibition in Human Cancers Carrying the B-RafV600E Mutation**

Huisheng Wang, Sherif Daouti, Wen-hui Li, Yang Wen, Christine Rizzo, Brian Higgins, Kathryn Packman, Neal Rosen, John F. Boylan, David Heimbroom, and Huifeng Niu

*Précis:* 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.

5546 **p53-Dependent BRCA1 Nuclear Export Controls Cellular Susceptibility to DNA Damage**

Juhong Jiang, Eddy S. Yang, Guochun Jiang, Somaira Newsheem, Hong Wang, Tong Wang, Yihan Wang, Dean Billheimer, A. Bapsi Chakravarthy, Melissa Brown, Bruce Haffty, and Fen Xia

*Précis:* This study suggests novel strategies to resensitize p53-deficient breast cancer cells to genotoxic chemotherapy by restoring nuclear shuttling which is dysfunctional in such cells.

## THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

5522 **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

*Précis:* 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.

5558 **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

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

5569 **YB-1 Bridges Neural Stem Cells and Brain Tumor-Initiating Cells via Its Roles in Differentiation and Cell Growth**

Abbas Fotovati, Samah Abu-Ali, Pei-Shan Wang, Loic P. Deleyrolle, Cathy Lee, Joanna Triscott, James Y. Chen, Sonia Franciosi, Yasuhiro Nakamura, Yasuo Sugita, Takeshi Uchiumi, Michihiko Kuwano, Blair R. Leavitt, Sheila K. Singh, Alexa Jury, Chris Jones, Hiroaki Wakimoto, Brent A. Reynolds, Catherine J. Pallen, and Sandra E. Dunn

*Précis:* 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.

## TUMOR AND STEM CELL BIOLOGY

5579

**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.

5588

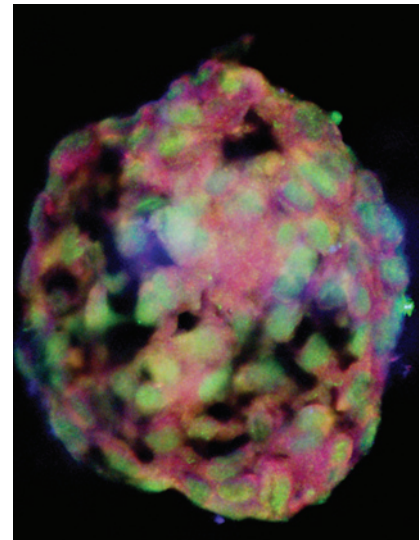
**p53-Dependent Regulation of Mitochondrial Energy Production by the RelA Subunit of NF- $\kappa$ B**

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.



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