### BREAKING ADVANCES

#### Highlights from Recent Cancer Literature

- **5055**
  - Title: Hedgehog Fights Back: Mechanisms of Acquired Resistance against Smoothened Antagonists
  - Authors: Ciara Metcalfe and Frederic J. de Sauvage

#### Chemotherapeutic Resistance: Surviving Stressful Situations

- **5062**
  - Authors: Luke A. Gilbert and Michael T. Hemann

### REVIEWS

#### Hedgehog Fights Back: Mechanisms of Acquired Resistance against Smoothened Antagonists

- **5057**
  - Authors: Ciara Metcalfe and Frederic J. de Sauvage

#### Chemotherapeutic Resistance: Surviving Stressful Situations

- **5062**
  - Authors: Luke A. Gilbert and Michael T. Hemann

### PRIORITY REPORTS

#### Combinatorial Treatments That Overcome PDGFRβ-Driven Resistance of Melanoma Cells to V600E-RAF Inhibition

- **5067**
  - Authors: Hubing Shi, Xiangju Kong, Antoni Ribas, and Roger S. Lo

#### Mechanical Stiffness Grades Metastatic Potential in Patient Tumor Cells and in Cancer Cell Lines

- **5075**

### CLINICAL STUDIES

#### Keap1 Mutations and Nrf2 Pathway Activation in Epithelial Ovarian Cancer

- **5081**
  - Authors: Panagiotis A. Konstantinopoulos, Dimitrios Spentzos, Elena Fountzilas, Nancy Francoeur, Srisowmya Sanisetty, Alexandros P. Grammatikos, Jonathan L. Hecht, and Stephen A. Cannistra

#### Tumor Microenvironment–Derived Proteins Dominate the Plasma Proteome Response during Breast Cancer Induction and Progression

- **5090**
  - Authors: Sharon J. Pitteri, Karen S. Kelly-Spratt, Kay E. Gurley, Jacob Kennedy, Tina Busald Buson, Alice Chin, Hong Wang, Qing Zhang, Chee-Hong Wong, Lewis A. Chodosh, Peter S. Nelson, Samir M. Hanash, and Christopher J. Kemp

### INTEGRATED SYSTEMS AND TECHNOLOGIES

#### Mechanical Stiffness Grades Metastatic Potential in Patient Tumor Cells and in Cancer Cell Lines

- **5075**

#### Myeloid-Derived Suppressor Cell Inhibition of the IFN Response in Tumor-Bearing Mice

- **5101**
  - Authors: Bethany L. Mundy-Bosse, Gregory B. Lesinski, Alexa C. Jaime-Ramirez, Kristen Bemninger, Mahmood Khan, Perianman Kuppusamy, Kristan Guenterberg, Sri Vidya Kondadasula, Abhik Ray Chaudhury, Krista M. La Perle, Melanie Kreiner, Gregory Young, Denis C. Guttridge, and William E. Carson, III

### MICROENVIRONMENT AND IMMUNOLOGY

#### Myeloid-Derived Suppressor Cell Inhibition of the IFN Response in Tumor-Bearing Mice

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  - Authors: Bethany L. Mundy-Bosse, Gregory B. Lesinski, Alexa C. Jaime-Ramirez, Kristen Bemninger, Mahmood Khan, Perianman Kuppusamy, Kristan Guenterberg, Sri Vidya Kondadasula, Abhik Ray Chaudhury, Krista M. La Perle, Melanie Kreiner, Gregory Young, Denis C. Guttridge, and William E. Carson, III
PD-1/PD-L1 Interactions Contribute to Functional T-Cell Impairment in Patients Who Relapse with Cancer After Allogeneic Stem Cell Transplantation


Précis: Findings show how leukemia cells can escape from graft-versus-tumor immune responses, and how interfering with this escape mechanism can restore antitumor immunity and possibly prevent relapses.

Systemic Cancer Therapy with a Small Molecule Agonist of Toll-like Receptor 7 Can Be Improved by Circumventing TLR Tolerance

Carole Bourquin, Christian Hotz, Daniel Noerenberg, Andreas Voelkl, Simon Heidegger, Bettina Storch, Nadja Sandholzer, Cornelia Wurzenberger, David Anz, and Stefan Endres

Précis: Findings offer insight into a cellular mechanism of immune tolerance that occurs during cancer immunotherapy with a Toll-like receptor agonist and provide a strategy to bypass this tolerance.

Antibody-Dependent Cell Cytotoxicity Synapses Form in Mice during Tumor-Specific Antibody Immunotherapy

Pascale Hubert, Adèle Heitzmann, Sophie Viel, André Nicolas, Xavier Sastre-Garau, Pablo Oppezzo, Otto Pritsch, Eduardo Osinaga, and Sebastian Amigorena

Précis: Findings demonstrate that a therapeutic monoclonal antibody specific for a ubiquitous tumor-associated antigen inhibits tumor growth via antibody-dependent cell toxicity.

IGFBP-3 Is a Metastasis Suppression Gene in Prostate Cancer


Précis: This study reports the first transgenic mouse model of spontaneous metastatic prostate cancer, a milestone that may help advance studies of progression and treatment at this deadly late stage of disease.

18F-Fluorodeoxy-glucose Positron Emission Tomography Marks MYC-Overexpressing Human Basal-Like Breast Cancers

Nicolaas Palaskas, Steven M. Larson, Nikolaus Schultz, Evangelia Komisopoulou, Justin Wong, Dan Rohle, Carl Campos, Nicolas Yannuzzi, Joseph R. Osborne, Irina Linkov, Edward R. Kastenhuber, Richard Taschereau, Seema B. Plaisier, Chris Tran, Adriana Heguy, Hong Wu, Chris Sander, Michael E. Phelpes, Cameron Brennan, Elisa Port, Jason T. Huse, Thomas G. Graeber, and Ingo K. Mellinghoff

Précis: FDG-PET may be useful as a noninvasive biomarker for therapies that target either the basal-like breast cancer subtype or MYC-overexpressing tumors that rely heavily upon glycolysis and the glutamine pathway.
BMP4 Promotes Prostate Tumor Growth in Bone through Osteogenesis
Yu-Chen Lee, Chien-Jui Cheng, Mehmet A. Bilen, Jing-Fang Lu, Robert L. Satcher, Li-Yuan Yu-Lee, Gary E. Gallick, Sankar N. Maity, and Sue-Hwa Lin

Précis: Osteogenesis is shown to be necessary for prostate cancer progression in bone and inhibition of this process may offer a treatment strategy for bone metastases.

Akt-Dependent Glucose Metabolism Promotes McI-1 Synthesis to Maintain Cell Survival and Resistance to Bcl-2 Inhibition
Jonathan L. Coloff, Andrew N. Macintyre, Amanda G. Nichols, Tingyu Liu, Catherine A. Gallo, David R. Plas, and Jeffrey C. Rathmell

Précis: Inhibition of glucose metabolism alters expression of a key Bcl-2 family member, sensitizing cancer cells to apoptosis and illustrating how strategies to disrupt glycolysis disruptions may disable tumors.

MicroRNA Replacement Therapy for miR-145 and miR-33a Is Efficacious in a Model of Colon Carcinoma
Ahmed Fawzy Ibrahim, Ulrike Weirauch, Maren Thomas, Arnold Grünweller, Roland K. Hartmann, and Achim Aigner

Précis: This study establishes nonviral miRNA replacement therapy for cancer treatment.

Combined Gene Expression Profiling and RNAi Screening in Clear Cell Renal Cell Carcinoma Identify PLK1 and Other Therapeutic Kinase Targets
Yan Ding, Dan Huang, Zhongfa Zhang, Josh Smith, David Petillo, Brendan D. Looyenga, Kristin Feenstra, Jeffrey P. MacKeigan, Kyle A. Furge, andBin T. Teh

Précis: RNAi screening and gene expression profiling reveal new potential therapeutic targets to treat highly aggressive kidney cancers.

Exosome Targeting of Tumor Antigens Expressed by Cancer Vaccines Can Improve Antigen Immunogenicity and Therapeutic Efficacy
Ryan B. Bountree, Stefanie J. Mandl, James M. Nachtwey, Katie Dalpozzo, Lisa Do, John R. Lombardo, Peter L. Schoonmaker, Kay Brinkmann, Ulrike Dirmeier, Reiner Laus, andAlain Delcayre

Précis: This study shows how engineering the MVA-BN-PRO vaccine to express its antigens in secreted exosomes could greatly improve its immunotherapeutic activity.

Retinoic Acid Enhances TRAIL-Induced Apoptosis in Cancer Cells by Upregulating TRAIL Receptor 1 Expression
Latha Dhandapani, Ping Yue, Suresh S. Ramalingam, Fadlo R. Khuri, and Shi-Yong Sun

Précis: By establishing that retinoic acid can stimulate the proapoptotic activity of TRAIL by upregulating the TRAIL receptor DR4, this study suggests a strategy to augment the anticancer activity of TRAIL being studied in clinical trials.

A Drug Resistance Screen Using a Selective MET Inhibitor Reveals a Spectrum of Mutations That Partially Overlap with Activating Mutations Found in Cancer Patients
Ralph Tiedt, Elisa Degenkolbe, Pascal Furet, Brent A. Appleton, Sabrina Wagner, Joseph Schoepfer, Emily Buck, David A. Budd, John E. Monahan, Michael D. Jones, Jutta Blank, Dorothea Haasen, Peter Drueckes, Markus Wartmann, Clive McCarthy, William R. Sellers, and Francesco Hofmann

Précis: Drug resistance mutation profiles reported in this manuscript are likely to predict clinical responses to MET kinase inhibitors, a number of which are currently in development.

Overcoming Hypoxia-Induced Apoptotic Resistance through Combinatorial Inhibition of GSK-3β and CDK1

Précis: Findings elucidate a novel therapeutic strategy to overcome the inherent resistance of hypoxic cancer cells to cell death, by targeting two kinases not previously linked to cell death protection in hypoxic tumor microenvironments.
Interleukin-1α Mediates the Antiproliferative Effects of 1,25-Dihydroxyvitamin D3 in Prostate Progenitor/Stem Cells
Sophia L. Maund, Wendy W. Barclay, Laura D. Hover, Linara S. Axanova, Guangchao Sui, Jason D. Hipp, James C. Fleet, Andrew Thorburn, and Scott D. Cramer

Precis: Supporting applications of vitamin D as a chemopreventative agent for prostate cancer, this study shows that the metabolically active form of vitamin D can induce differentiation and senescence of prostate progenitor/stem cells and that its antiproliferative effects rely upon interleukin-1 alpha.

PTEN Positively Regulates UVB-Induced DNA Damage Repair
Mei Ming, Li Feng, Christopher R. Shea, Keyoumars Soltani, Baozhong Zhao, Weonong Han, Robert C. Smart, Carol S. Trempus, and Yu-Ying He

Precis: Findings explain how failure to repair DNA damage caused by UVB sunlight radiation can cause skin carcinogenesis, due to inactivation of the tumor suppressor PTEN that destroys its key gatekeeper function in supporting DNA repair in the skin.

IL-8 Signaling Plays a Critical Role in the Epithelial–Mesenchymal Transition of Human Carcinoma Cells
Romaine I. Fernando, Marianne D. Castillo, Mary Litzinger, Duane H. Hamilton, and Claudia Palena

Precis: Findings elucidate the role of epithelial-to-mesenchymal transition in the modulation of the tumor microenvironment, suggesting that IL-8 signaling blockades might be very effective at targeting invasive tumor cells.

ABCB5 Identifies a Therapy-Refractory Tumor Cell Population in Colorectal Cancer Patients
Brian J. Wilson, Tobias Schatton, Qian Zhan, Martin Gasser, Jie Ma, Karim R. Saab, Robin Schanche, Ana-Maria Waaga-Gasser, Jason S. Gold, Qin Huang, George F. Murphy, Markus H. Frank, and Natasha Y. Frank

Precis: Findings point to the need to eradicate a particular tumor cell population to improve outcomes in colorectal cancer therapy.

Cancer Stem Cells in SQUAMOUS CELL CARCINOMA Switch between Two Distinct Phenotypes That Are Preferentially Migratory or Proliferative
Adrian Biddle, Xiao Liang, Luke Gammon, Bilal Fazil, Lisa J. Harper, Helena Emich, Daniela Elena Costea, and Ian C. Mackenzie

Precis: Findings suggest that cancer stem cells can switch their phenotype between two states that can either drive tumor cell proliferation or metastatic dissemination, implying a need for therapeutic approaches that are able to eradicate cancer stem cells in both states.

ADP-Ribosylarginine Hydrolase Regulates Cell Proliferation and Tumorigenesis
Jiro Kato, Jianfeng Zhu, Chengyu Liu, Mario Stylianou, Victoria Hoffmann, Martin J. Lizak, Connie G. Glasgow, and Joel Moss

Precis: Findings point to an important role for posttranslational protein modification by ADP-ribosylation in supporting cell proliferation and tumorigenesis.

Sequential Activation of Snail1 and N-Myc Modulates Sonic Hedgehog–Induced Transformation of Neural Cells
Leah E. Colvin Wanshura, Katherine E. Galvin, Hong Ye, Martin E. Fernandez-Zapico, and Cynthia Wetmore

Precis: N-Myc activation by a key target of the Sonic Hedgehog signaling pathway may be an essential step in the information of an aggressive class of pediatric brain tumors, with implications for therapeutic targeting strategies.

Microvesicles Released from Human Renal Cancer Stem Cells Stimulate Angiogenesis and Formation of Lung Premetastatic Niche
Cristina Grange, Marta Tapparo, Federica Collino, Lorian Vitillo, Christian Damasco, Maria Chiara Deregibus, Ciro Tetta, Benedetta Bussolati, and Giovanni Camussi

Precis: Cancer stem cells may promote metastatic progression by secreting a class of microvesicles known as exosomes that can transfer proangiogenic RNAs to endothelial cells and directly stimulate angiogenesis.
LETTERS TO THE EDITOR

5357 MicroRNA Expression and Outcome in Resected NSCLC—Letter
Shun-ichiro Kageyama, Yusuke Takagi, Takeshi Sawada, Natsuko Kageyama-Yahara, and Masahiko Shibuya

5358 MicroRNA Expression and Outcome in Resected NSCLC—Response
Johannes Voortman, Aaron J. Schetter, Curtis C. Harris, and Giuseppe Giaccone

CORRECTIONS

5360 Correction: Effects of Carbon Ion Beam on Putative Colon Cancer Stem Cells and Its Comparison with X-rays

5361 Correction: A Requirement of STAT3 DNA Binding Precludes Th-1 Immunostimulatory Gene Expression by NF-κB in Tumors

ABOUT THE COVER

The search for biomarkers of cancer has focused on the tumor cells themselves. Pitteri and colleagues, using an unbiased and in depth proteomic analysis of plasma from a model of Her2/neu driven breast cancer, have identified the signaling between the tumor cells and microenvironment as a primary source of biomarkers. Shown are tumor cells embedded within extensive extracellular collagen matrix stained with trichrome blue. For details, see the article by Pitteri and colleagues on page 5090 of this issue.