**REVIEW**

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

**Chemotherapeutic Resistance: Surviving Stressful Situations**
Luke A. Gilbert and Michael T. Hemann

**PRIORITY REPORTS**

**Combinatorial Treatments That Overcome PDGFRβ-Driven Resistance of Melanoma Cells to V600E-RAF Inhibition**
Hubing Shi, Xiangju Kong, Antoni Ribas, and Roger S. Lo

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

**CLINICAL STUDIES**

**Keap1 Mutations and Nrf2 Pathway Activation in Epithelial Ovarian Cancer**
Panagiotis A. Konstantinopoulos, Dimitrios Spentzos, Elena Fountzilas, Nancy Francoeur, Srismoyna Sanisety, Alexandros P. Grammatikos, Jonathan L. Hecht, and Stephen A. Cannistra

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

**MICROENVIRONMENT AND IMMUNOLOGY**

**Myeloid-Derived Suppressor Cell Inhibition of the IFN Response in Tumor-Bearing Mice**
Bethany L. Mundy-Bosse, Gregory B. Lesinski, Alena C. Jaime-Ramirez, Kristen Benninger, Mahmood Khan, Perianman Kuppusamy, Kristan Guenterberg, Sri Vidy Kondadasula, Abhik Ray Chaudhury, Krista M. La Perle, Melanie Kreiner, Gregory Young, Denis C. Guttridge, and William E. Carson, III

**Précis:** This study illustrates the great importance of the interplay between clinical and laboratory-based research in responding rapidly to the inevitable problem of acquired resistance arising in the development of any new targeted treatment for cancer.

**Précis:** Findings reveal a key molecular determinant of resistance to platinum-based chemotherapy and poor clinical outcome in patients with epithelial ovarian cancers.

**Précis:** Dynamic interactions between tumor cells and their host microenvironment are reflected by changes in the plasma proteome, offering new opportunities for cancer diagnosis.

**Précis:** Myeloid derived suppressor cells blunt immune cell responsiveness to interferons by producing reactive nitrogen species, which attenuates interferon signaling in immune cells of tumor-bearing animals.
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 Osínaga, and Sébastien 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

Nicolaos 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 Tashchereau, Seema B. Plaisier, Chris Tran, Adriana Hегу, Hong Wu, Chris Sander, Michael E. Phelps, 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.

Inhibition of miR-193a Expression by Max and RXRa Activates K-Ras and PLAU to Mediate Distinct Aspects of Cellular Transformation

Dimitrios Ililiopoulos, Asaf Rotem, and Kevin Struhl

Précis: Findings describe a molecular pathway involved in cellular transformation that focuses on miR-193a as a regulator of both tumorigenicity and invasiveness.

Combining Betulinic Acid and Mithramycin A Effectively Suppresses Pancreatic Cancer by Inhibiting Proliferation, Invasion, and Angiogenesis

Yong Gao, Zhiliang Jia, Xiangyu Kong, Qiang Li, David Z. Chang, Daoyan Wei, Xiangdong Le, Shengdong Huang, Liwei Wang, Suyun Huang, and Keping Xie

Précis: Findings demonstrate that targeting the transcription factor Sp1 can inhibit pancreatic tumor growth with greater efficacy and fewer side effects than traditional treatment.

Genetic Variation in an miRNA-1827 Binding Site in MYCL1 Alters Susceptibility to Small-Cell Lung Cancer

Fang Xiong, Chen Wu, Jiang Chang, Dianke Yu, Binghe Xu, Peng Yuan, Kai Zhai, Jian Xu, Wen Tan, and Dongxin Lin

Précis: Findings suggest a broader significance than appreciated previously for the L-MYC gene in development of small cell lung cancer.
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<td>A Drug Resistance Screen Using a Selective MET Inhibitor Reveals a Spectrum of Mutations That Partially Overlap with Activating Mutations Found in Cancer Patients</td>
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<td>Overcoming Hypoxia-Induced Apoptotic Resistance through Combinatorial Inhibition of GSK-3β and CDK1</td>
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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 Su, 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, Weining 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 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, Loriana Vitillo, Christian Dasamo, Maria Chiara Derenbergus, 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

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## 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.

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