## BREAKING ADVANCES

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**Highlights from Recent Cancer Literature**

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## REVIEWS

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**The Next Challenge in Cancer Immunotherapy: Controlling T-Cell Traffic to the Tumor**

Jean-Pierre Abastado

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**T-Regulatory Cells: Key Players in Tumor Immune Escape and Angiogenesis**

Andrea Facciabene, Gregory T. Motz, and George Coukos

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## MEETING REPORT

2172

**Systems Biology of Tumor Dormancy: Linking Biology and Mathematics on Multiple Scales to Improve Cancer Therapy**

Heiko Enderling, Philip Hahnfeldt, Lynn Hlatky, and Nava Almog

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## PRIORITY REPORTS

2176

**Interactions of Abiraterone, Eplerenone, and Prednisolone with Wild-type and Mutant Androgen Receptor: A Rationale for Increasing Abiraterone Exposure or Combining with MDV3100**

Juliet Richards, Ai Chinn Lim, Colin W. Hay, Angela E. Taylor, Anna Wingate, Karolina Nowakowska, Carmel Pesaro, Suzanne Carreira, Jane Goodall, Wiebke Arlt, Iain J. McEwan, Johann S. de Bono, and Gerhardt Attard

Précis: The administration of corticoid drugs intended to reduce the side effects of abiraterone in the treatment of castration-resistant prostate cancer can actually lead to disease progression via activation of wild-type or mutant androgen receptor.

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2183

**Bone Marrow Stromal Cells Create a Permissive Microenvironment for Myeloma Development: A New Stromal Role for Wnt Inhibitor Dkk1**

Jessica A. Fowler, Gregory R. Mundy, Seint T. Lwin, and Claire M. Edwards

Précis: Findings define a pivotal role for the Wnt inhibitor Dkk1 in the stromal cells of the bone marrow microenvironment, which supports development of deadly myeloma blood tumors.

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## CLINICAL STUDIES

2197

**Epigenetic Resensitization to Platinum in Ovarian Cancer**

Daniela Matei, Fang Fang, Changuy Shen, Jeanne Schilder, Alesha Arnold, Yan Zeng, William A. Berry, Tim Huang, and Kenneth P. Nephew

Précis: Findings of this phase II clinical trial support the use of DNA methylation-based epigenetic therapies to resensitize drug-resistant tumors to cytotoxic chemotherapy, addressing one of the most important challenges in the oncology clinic.

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2206

**A RASSF1A Polymorphism Restricts p53/p73 Activation and Associates with Poor Survival and Accelerated Age of Onset of Soft Tissue Sarcoma**

Karen S. Yee, Lukasz Grochola, Garth Hamilton, Anna Gawenda, Elisabeth E. Bond, Helge Taubert, Peter Wurl, Gareth L. Bond, and Eric O’Neill

Précis: This study provides a mechanistic description of a coding SNP in the Ras family member RASSF1A that correlates with survival and onset of disease in soft-tissue sarcoma patients, offering a simple host prognostic marker in this setting.

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## INTEGRATED SYSTEMS AND TECHNOLOGIES

2218

**Reconsidering the Paradigm of Cancer Immunotherapy by Computationally Aided Real-time Personalization**

Yuri Kogan, Karin Halevi-Tobias, Moran Elshmereni, Stanimir Vuk-Pavlović, and Zvia Agur

Précis: It may be possible to personalize cancer immunotherapy and immunochemotherapy based on mathematical models that are validated early in the treatment process, thereby enabling an adaptive personalized regimen during the treatment period.
A Galectin-3–Dependent Pathway Upregulates Interleukin-6 in the Microenvironment of Human Neuroblastoma
Ayaka M. Silverman, Rie Nakata, Hiroyuki Shimada, Richard Sposto, and Yves A. DeClerck

Precis: This study reveals that a regulator of immune escape in the tumor microenvironment regulates the proinflammatory cytokine IL-6, a pivotal modifier of cancer progression.

Tumor Angiogenesis Mediated by Myeloid Cells Is Negatively Regulated by CEACAM1
Rongze Lu, Maciej Kujawski, Hao Pan, and John E. Shively

Precis: A cell-surface receptor on myeloid cells that inhibits tumor growth is found to restrict production of a proangiogenic growth factor that promotes the growth of the tumor vasculature.

Chromatin Remodeling Underlies the Senescence-Associated Secretory Phenotype of Tumor Stromal Fibroblasts That Supports Cancer Progression
Ermira Pazolli, Elishe Aslach, Agnieszka Milczarek, Julie Prior, David Pwnica-Worms, and Sheila A. Stewart

Precis: A significant part of the risk provided by aging in cancer may be derived from the contributions of senescing stromal fibroblasts that fuel malignant progression through at least 2 independent signaling cascades activated in response to chromatin changes.

Genetic Ablation of Cav1 Differentially Affects Melanoma Tumor Growth and Metastasis in Mice: Role of Cav1 in Shh Heterotypic Signaling and Transendothelial Migration
Franco Capozza, Casey Trimmer, Remedios Castello-Cros, Sanjay Katiyar, Diana Whitaker-Menezes, Antonia Follenzi, Marco Crosario, Gemma Llaverias, Federica Sotgia, Richard G. Pestell, and Michael P. Lisanti

Precis: Reinforcing the need to study cancer in an organonal context to gain deeper understanding, a core scaffolding protein in lipid rafts is found to regulate the growth of primary tumors and metastases quite differently.

The SUMO E3-ligase PIA1 Regulates the Tumor Suppressor PML and Its Oncogenic Counterpart PML-RARA
Andrea Rabelino, Brandon Carter, Georgia Konstantinidou, Shwu-Yuan Wu, Alessandro Rimessi, Lauren A. Byers, John V. Heymach, Luc Girard, Cheng-Ming Chiang, Julie Teruya-Feldstein, and Pier Paolo Scaglioni

Precis: Findings offer mechanistic insights into how the sumoylation machinery modifies oncogenic signals regulated by the tumor suppressor PML, and also the therapeutic response to leptomias involving PML mutations.

Hypoxia-Inducible Factor-2α Activation Promotes Colorectal Cancer Progression by Dysregulating Iron Homeostasis
Xiang Xue, Matthew Taylor, Erik Anderson, Cathy Hao, Aluuan Qu, Joel K. Greenston, Ellen M. Zimmermann, Frank J. Gonzalez, and Yatirk M. Shah

Precis: This study points to an intestinal iron transporter as a tractable candidate target for colon cancer therapy.

Defining NOTCH3 Target Genes in Ovarian Cancer
Xu Chen, Michelle M. Thiaville, Li Chen, Alexander Stoeck, Jianhua Xuan, Min Gao, Ie-Ming Shih, and Tian-Li Wang

Precis: Target genes regulated by Notch3 are of interest given emerging evidence of a role for this receptor in programming cancer stem-like cell behavior in lung and ovarian cancers.

Intragenic ATM Methylation in Peripheral Blood DNA as a Biomarker of Breast Cancer Risk
Kevin Brennan, Montserrat Garcia-Closas, Nick Orr, Olivia Fletcher, Michael Jones, Alan Ashworth, Anthony Swerdlow, Heather Thorne on behalf of KConFab Investigators, Eli Riboli, Paolo Vinesi, Miren Dorronsoro, Francaise Clavel-Chapelon, Salvatore Panico, N. Charlotte Onland-Moret, Dimitrios Trichopoulos, Rudolf Kaaks, Kay-Tee Khaw, Robert Brown, and James M. Flanagan

Precis: As cancer risk studies move from genome to epigenome associations, the use of DNA isolated from peripheral blood cells offers an easily accessible sample type for epigenome-wide association studies.
Effects of a Caloric Restriction Weight Loss Diet and Exercise on Inflammatory Biomarkers in Overweight/Obese Postmenopausal Women: A Randomized Controlled Trial
Ikuyo Imayama, Cornelia M. Ulrich, Catherine M. Alfano, Chiachi Wang, Liren Xiao, Mark H. Wener, Kristin L. Campbell, Catherine Duggan, Karen E. Foster-Schubert, Angela Kong, Caitlin E. Mason, Ching-Yun Wang, George L. Blackburn, Carolyn E. Bain, Henry J. Thompson, and Anne McTiernan

Précis: Findings suggest that weight loss with or without exercise may reduce risk of breast cancer, possibly due to a reduction in systemic inflammation that may support tumor development or progression.

Impact of Intertumoral Heterogeneity on Predicting Chemotherapy Response of BRCA1-Deficient Mammary Tumors

Précis: Studies of BRCA1-deficient mammary cancers suggest that tumor heterogeneity makes it difficult to define gene expression signatures that could predict chemotherapy responses.

Immune Response Is an Important Aspect of the Antitumor Effect Produced by a CD40L-Encoding Oncolytic Adenovirus
Iulia Diaconu, Vincenzo Cerullo, Mari L.M. Hirvinen, Sophie Escutenaire, Matteo Ugolini, Salla K. Pesonen, Simona Bramante, Savi Parvainen, Anna Kanerva, Angelica S.I. Loskog, Aristides G. Elioopoulos, Sari Pesonen, and Aksei Hemminki

Précis: Findings detail the development of a new generation of oncolytic adenovirus that is armed with CD40L, which results in the induction of a TH1-type immune response that causes accumulation of cytotoxic T cells at the tumor site and increased antitumor efficacy.

Novel MT1-MMP Small-Molecule Inhibitors Based on Insights into Hemopexin Domain Function in Tumor Growth
Albert G. Remacle, Vladislav S. Golubkov, Sergey A. Shiryayev, Russell Dahl, John L. Stebbins, Andrei V. Chernov, Anton V. Cheltsov, Maurizio Pellecchia, and Alex Y. Strongin

Précis: Findings reveal that targeting a regulatory domain of increasing pharmacologic interest in matrix metalloproteases and other proteins can exert potent antitumor properties.

Expression of the p53 Target CDIP Correlates with Sensitivity to TNFα-Induced Apoptosis in Cancer Cells
Lauren Brown-Endres, David Schoenfeld, Fang Tian, Hyung-Gu Kim, Takushi Namba, César Muñoz-Fontela, Anna Mandinova, Stuart A. Aaronson, and Sam W. Lee

Précis: This study suggests that the product of a p53 target gene may serve as a predictive biomarker for TNF-based cancer therapeutics.

S-Glutathionylated Serine Proteinase Inhibitors as Plasma Biomarkers in Assessing Response to Redox-Modulating Drugs

Précis: Novel blood-based biomarkers will assist in pharmacogenetic design of protocols that test new drugs.
### TUMOR AND STEM CELL BIOLOGY

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<td>Dithiolethiones Inhibit NF-κB Activity via Covalent Modification in Human Estrogen Receptor–Negative Breast Cancer</td>
<td>Christopher H. Switzer, Robert Y.-S. Cheng, Lisa A. Ridnour, Margaret C. Murray, Valerio Tazzari, Anna Sparatore, Piero Del Soldato, Harry B. Hines, Sharon A. Glynn, Stefan Ambs, and David A. Wink</td>
<td>A novel chemical mechanism to inhibit NF-κB activation in aggressive estrogen receptor-negative breast cancers may blunt their invasive capabilities.</td>
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<td>2405</td>
<td>p120RasGAP-Mediated Activation of c-Src Is Critical for Oncogenic Ras to Induce Tumor Invasion</td>
<td>Po-Chao Chan and Hong-Chen Chen</td>
<td>The requirement for c-Src in tumor invasion evoked by oncogenic Ras has implications for the development of therapies to target the Ras pathway, a long goal of the field.</td>
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<td>2416</td>
<td>Estrogen Receptor Alpha Mediates Progestin-Induced Mammary Tumor Growth by Interacting with Progesterone Receptors at the Cyclin D1/MYC Promoters</td>
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<td>Antiestrogens block progesterone-induced tumor growth because they disrupt estrogen receptor–progesterone receptor interactions that are essential for target gene transcription.</td>
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<td>Proteomic Portrait of Human Breast Cancer Progression Identifies Novel Prognostic Markers</td>
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<td>In performing the deepest proteomic analysis of breast cancer progression to date, this study identifies novel prognostic markers for overall survival that function in metabolic and secretory processes.</td>
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<td>Suppression of the Epithelial–Mesenchymal Transition by Grainyhead-like-2</td>
<td>Benjamin Cieply, Philip Riley IV, Phillip M. Pifer, Joseph Widmeyer, Joseph B. Addison, Alexey V. Ivanov, James Denvir, and Steven M. Frisch</td>
<td>A gene involved in wound healing and neural tube closure is found to be a suppressor of oncogenic epithelial–mesenchymal transition, a pivotal process in cancer cells that is tightly associated with the capacity for metastatic progression.</td>
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### ABOUT THE COVER

Galectin-3 binding protein, a glycoprotein produced by neuroblastoma cells, upregulates the expression of interleukin-6 in bone marrow mesenchymal cells by interacting with galectin-3. Using immunofluorescence, it was found that the galectin-3 binding protein colocalizes with galectin-3 at the surface and in the cytosol of mesenchymal cells. This interaction generates a Ras/MEK/ERK-dependent signal that transcriptionally upregulates the production of interleukin-6 in the bone marrow microenvironment. Activation of this pathway contributes to neuroblastoma bone metastasis. For details, see article by Silverman and colleagues on page 2228 of this issue.