BREAKING ADVANCES

Highlights from Recent Cancer Literature

POINT–COUNTERPOINT REVIEWS

RECIST: No Longer the Sharpest Tool in the Oncology Clinical Trials Toolbox—Point
Manish R. Sharma, Michael L. Maitland, and Mark J. Ratain
See Counterpoint and Reply by Fojo and Noonan, p. 5151 and p. 5150

RECIST: No Longer the Sharpest Tool in the Oncology Clinical Trials Toolbox—Reply to Point
Antonio T. Fojo and Anne Noonan
See Point by Sharma et al., p. 5145

Why RECIST Works and Why It Should Stay—Counterpoint
Antonio T. Fojo and Anne Noonan
See Point and Reply by Sharma et al., p. 5145 and p. 5158

Why RECIST Works and Why It Should Stay—Reply to Counterpoint
Manish R. Sharma, Michael L. Maitland, and Mark J. Ratain
See Counterpoint by Fojo and Noonan, p. 5151

MEETING REPORT

Changing the Tumor Microenvironment: New Strategies for Immunotherapy
Pedro Berraondo, Viktor Umansky, and Ignacio Melero

PRIORITY REPORTS

RALBP1/RLIP76 Depletion in Mice Suppresses Tumor Growth by Inhibiting Tumor Neovascularization
Seunghyung Lee, Jeremy G. T. Wurtzel, Sharad S. Singhal, Sanjay Awashti, and Lawrence E. Goldfinger
Précis: A widely expressed multifunctional protein that binds to Ral and R-Ras small GTPases is essential to support the blood vasculature in tumors, supporting its candidacy as a generalized anticancer target.

INTEGRATED SYSTEMS AND TECHNOLOGIES

An NMR Metabolomics Approach for the Diagnosis of Leptomeningeal Carcinomatosis
Hye Rim Cho, He Wen, Young Jin Ryu, Yong Jin An, Hyo Cheol Kim, Woo Kyung Moon, Moon Hee Han, Sunghyouk Park, and Seung Hong Choi
Précis: Preclinical proof-of-concept for metabolic typing of cerebral spinal fluid offers a tool to improve diagnostic accuracy of one of the more common types of metastatic invasion into the central nervous system, immediately prompting clinical testing of this approach.

MICROENVIRONMENT AND IMMUNOLOGY

Impaired IFN-α Production by Plasmacytoid Dendritic Cells Favors Regulatory T-cell Expansion That May Contribute to Breast Cancer Progression
Vanja Sisirak, Julien Faget, Michael Gobert, Nadège Goutagny, Nelly Vey, Isabelle Treilleux, Sarah Benaudineau, Gisèle Poyet, Sana Intidhar Labidi-Galy, Sophie Godard-Leon, Isabelle Durand, Isabelle Le Mercier, Agathe Bajard, Thomas Bachelot, Alain Puisieux, Isabelle Puisieux, Jean-Yves Blay, Christine Ménétrier-Caux, Christophe Caux, and Nathalie Bendriss-Vermare
Précis: This study unravels the mechanistic basis for the negative impact of pDC infiltration in breast tumor and offers perspectives for new therapeutic strategies by targeting pDC to overcome immune tolerance in breast cancer.
Stromal Progenitor Cells from Endogenous Adipose Tissue Contribute to Pericytes and Adipocytes That Populate the Tumor Microenvironment
Yan Zhang, Alexes C. Daquinag, Felipe Amaya-Manzanares, Olga Sirin, Chieh Tseng, and Mikhail G. Kolonin

Precis: This report suggests that obesity promotes cancer progression by providing a wellspring of adipose cells for tumors to recruit to their microenvironment, where they support angiogenesis and malignant outgrowth.

5209

PD-1 Blockade Enhances T-cell Migration to Tumors by Elevating IFN-γ Inducible Chemokines
Weiyi Peng, Chengwen Liu, Chunyu Xu, Yanyan Lou, Jieqing Chen, Yan Yang, Hideo Yagita, Willem W. Overwijk, Gregory Lizée, Laszlo Radvanyi, and Patrick Hwu

Precis: Blocking immune escape mechanisms mediated by the PD-1 pathway may enhance a variety of cancer therapies, including adoptive T-cell treatments that have shown promise over the years but induce durable responses in a minority of patients.

5219

TNF-α Mediates Macrophage-Induced Bystander Effects through Netrin-1
Yonghong Yang, Xingmin Wang, Danny R. Moore, Stanley A. Lightfoot, and Mark M. Huecke

Precis: Commensal intestinal infections that may program inflammation in the colon tumor microenvironment influence a neuronal pathway with emerging importance in cancer.

5230

A Retinoic Acid–Rich Tumor Microenvironment Provides Clonal Survival Cues for Tumor-Specific CD8⁺ T Cells
Yanxia Guo, Karina Pino-Lagos, Cory A. Ahonen, Kathy A. Bennett, Jinshan Wang, Joseph L. Napoli, Rune Blomhoff, Shanthini Sockanathan, Roshantha A. Chandraaratna, Ethan Dmitrovsky, Mary Jo Turk, and Randolph J. Noelle

Precis: These findings reveal that tumor growth elevates retinoic acid within the tumor microenvironment and that this event is critical to maintain tumor-specific CD8⁺ T-cell clonal survival and to facilitate antitumor immunity, with mechanistic implications for immunovigilant.

5240

Plasmacytoid Dendritic Cells Promote Immunosuppression in Ovarian Cancer via ICOS Costimulation of Foxp3⁺ T-Regulatory Cells
Curdin Conrad, Josh Gregorio, Yi-Hong Wang, Tomoki Ito, Stephan Meller, Shino Hanabuchi, Sonya Anderson, Neely Atkinson, Pedro T. Ramírez, Yong-Jun Liu, Ralph Freedman, and Michel Gillet

Precis: Findings identify a signaling pathway controlled by the T-cell coreceptor ICOS as a pivotal driver of immunosuppression in ovarian cancer.

5250

53BP1 Is a Haploinsufficient Tumor Suppressor and Protects Cells from Radiation Response in Glioma
Massimo Squatrito, Fabio Vanoli, Nikolaus Schultz, Maria Jasin, and Eric C. Holland

Precis: These findings suggest that components of the nonhomologous end-joining system of DNA repair may be good therapeutic targets to improve treatment of aggressive brain tumors.

5261

Clusterin Mediates TGF-β–Induced Epithelial–Mesenchymal Transition and Metastasis via Twist1 in Prostate Cancer Cells
Masaki Shiotia, Anousheh Zardan, Ario Takeuchi, Masafumi Kumano, Eliana Beraldi, Seiji Naito, Amina Zoubeidi, and Martin E. Gleave

Precis: These findings identify a new link between TGF-β and the epithelial–mesenchymal transition that could be targeted to block prostate cancer metastasis.

5273

Multilevel Whole-Genome Analysis Reveals Candidate Biomarkers in Clear Cell Renal Cell Carcinoma
Andrew H. Girgis, Vladimir V. Iakovlev, Ben Beheshti, Jane Bayani, Jeremy A. Squire, Anna Bui, Marina Mankaruo, Youssef Yousef, Bishoy Khalil, Heba Khella, Maria Pasic, and George M. Yousef

Precis: In addition to mutation and expression analyses, the analysis of gene methylation and gene-copy number as part of an integrated whole-genome analysis may provide a more comprehensive understanding of cancer heterogeneity to improve diagnosis, prognosis, and therapy.
**Hypoxia-Induced Gene Expression in Chemoradioresistant Cervical Cancer Revealed by Dynamic Contrast-Enhanced MRI**

Cathinka Halle, Erlend Andersen, Malin Lando, Eva-Katrine Jarnes, Grete Hasvold, Marit Holden, Randi G. Syljuasen, Kolbein Sundfør, Gunnar B. Kristensen, Ruth Holm, Eirik Malinen, and Heidi Lyng

**Pécisse:** A noninvasive imaging strategy has been found to identify patients who might benefit from hypoxic modification of chemoradiotherapy in cervical cancers.

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**Protein Tyrosine Phosphatase Shp2 (Ptpn11) Plays an Important Role in Maintenance of Chromosome Stability**

Xia Liu, Hong Zheng, and Cheng-Kui Qu

**Pécisse:** These findings reveal how deregulation of an important tyrosine phosphatase that modifies many pathways of cancer cell signaling contributes to malignant development.

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**Molecular Subsets of Mantle Cell Lymphoma Defined by the IGHV Mutational Status and SOX11 Expression Have Distinct Biologic and Clinical Features**


**Pécisse:** This large multidisciplinary study of mantle cell lymphoma reveals 2 previously unrecognized subtypes that may have distinct origins and clinical implications.

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**In Vivo Regulation of TGF-β by R-Ras2 Revealed through Loss of the RasGAP Protein NFI**

Deanna M. Patmore, Sara Welch, Patricia C. Fulkerst, Jangjiang Wu, Kwangmin Choi, David Eaves, Jennifer J. Kordich, Margaret H. Collins, Timothy P. Cripe, and Nancy Ratner

**Pécisse:** Findings that link the functions of TGF-β and R-Ras2/TC21, a little-studied member of the Ras superfamily, might explain why TGF-β suppresses tumors at early stages of development but later acts to promote tumor progression.

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**Prevention and Epidemiology**

**Leptin and Soluble Leptin Receptor in Risk of Colorectal Cancer in the European Prospective Investigation into Cancer and Nutrition Cohort**


**Pécisse:** Elucidation of the etiologic pathways linking obesity and colorectal cancer risk may improve risk assessment and opportunities for lifestyle interventions.

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**Therapeutics, Targets, and Chemical Biology**

**ROCK1 and ROCK2 Are Required for Non-Small Cell Lung Cancer Anchorage-Independent Growth and Invasion**

Domino Vigil, Tai Young Kim, Ana Plachco, Andrew J. Garton, Linda Castaldo, Jonathan A. Pachter, Hanqing Dong, Xin Chen, Brianna Tokar, Sharon L. Campbell, and Channing J. Der

**Pécisse:** These findings define a specific small-molecule inhibitor of the Rho kinases and reveal the potential therapeutic benefits of targeting them in a model of lung adenocarcinoma.

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**Sorafenib Has Potent Antitumor Activity against Multiple Myeloma In Vitro, Ex Vivo, and In Vivo in the 5T33MM Mouse Model**

Pedram Kharazibeh, Hendrik De Raeye, Charlotte Fristedt, Qiao Li, Astrid Gruber, Per Johnsson, Georgia Kokaraki, Maria Panzar, Edward Laane, Anders Osterborg, Boris Zhitovotsky, Helena Jernberg-Wiklund, Dan Grandé, Fredrik Celsing, Magnus Björkholm, Karin Vanderkerken, and Theocharis Panaretakis

**Pécisse:** Sorafenib, an approved broad-spectrum kinase inhibitor, might be repositioned to treat multiple myeloma, a highly aggressive cancer.
Natural Product Triptolide Mediates Cancer Cell Death by Triggering CDK7-Dependent Degradation of RNA Polymerase II
Stefano Giustino Manzo, Zhao-Li Zhou, Ying-Qing Wang, Jessica Marinello, Jin-Xue He, Yuan-Chao Li, Jian Ding, Giovanni Capranico, and Ze-Hong Miao

Précis: This study offers an explanation for how a key component of traditional Chinese medicine may mediate diverse medical effects, including anticancer effects.

GF-15, a Novel Inhibitor of Centrosomal Clustering, Suppresses Tumor Cell Growth In Vitro and In Vivo
Marc S. Raab, Iris Breitkreutz, Simon Anderhub, Mads H. Rønnest, Blanka Leber, Thomas O. Larsen, Ludmila Weiz, Gleb Konotop, Patrick J. Hayden, Klaus Podar, Johannes Fuehrer, Felix Nissen, Walter Mier, Uwe Haberkorn, Anthony D. Ho, Hartmut Goldschmidt, Kenneth C. Anderson, Mads H. Clausen, and Alwin Krämer

Précis: This study reports the characterization of a first-in-class inhibitor of centrosomal clustering and its unique mechanistic approach to cancer cell killing.

Mammalian Sterile 20–like Kinase 1 Suppresses Lymphoma Development by Promoting Faithful Chromosome Segregation
Tae-Shin Kim, Da-Hye Lee, Sang Kyum Kim, So Youn Shin, Eul-Ju Seo, and Dae-Sik Lim

Précis: The Hippo pathway has been implicated in oncogenesis of solid tumors, but these findings reveal that its core component may exert a tumor-suppressive function in blood cell tumors based on its ability to prevent chromosomal instability in lymphocytes.

The Unfolded Protein Response Induces the Angiogenic Switch in Human Tumor Cells through the PERK/ATF4 Pathway
Yugang Wang, Goleeta N. Alam, Yu Ning, Fernanda Visioli, Zhihong Dong, Jacques E. Nör, and Peter J. Polverini

Précis: These results offer new mechanistic insights into the links between angiogenesis and the unfolded protein response, which may be activated nearly universally in cancer cells.

Inhibition of Stathmin1 Accelerates the Metastatic Process
Karin Williams, Ritwik Ghosh, Premkumar Vummidi Giridhar, Guanyu Gu, Thomas Case, Scott M. Belcher, and Susan Kasper

Précis: These findings challenge the concept of stathmin as a cancer-promoting protein with evidence that it can restrain the invasive movement of metastatic cancer cells.

Inactivating All Three Rb Family Pocket Proteins Is Insufficient to Initiate Cervical Cancer
Myeong-Kyun Shin, Julien Sage, and Paul F. Lambert

Précis: These results provide a powerful argument that the HPV E7 oncoprotein drives cancer by binding to proteins other than the Rb family members, challenging central and long-standing assumptions in the field.

Melanoma Cells Inhibit NK Cell Functions—Letter
Giuseppe Sconocchia, Roberto Arriga, Luigi Tornillo, Luigi Terracciano, Soldano Ferrone, and Giulio C. Spagnoli

Melanoma Cells Inhibit NK Cell Functions—Response
Gabriella Pietra, Massimo Vitale, Claudia Manzini, Mirna Balsamo, Lorenzo Moretta, and Maria Cristina Mingari

Correction: Combination Therapy with HSP90 Inhibitor 17-DMAG Reconditions the Tumor Microenvironment to Improve Recruitment of Therapeutic T Cells

LETTERS TO THE EDITOR
ABOUT THE COVER

Obesity, caused by overgrowth of fat tissue, was shown to be associated with expansion and mobilization of adipose progenitor cells and with increased tumor growth. Animal experiments show that adipose progenitors are recruited by tumors, where they incorporate into the blood vessels and differentiate into adipocytes. A confocal section micrograph of a breast tumor grown in an obese mouse shows vascular/perivascular cells and adipocytes derived from GFP-labeled (green) adipose cells. Vascular endothelium was costained with a CD31 antibody (red), while nuclear staining (blue) identified malignant cells lacking GFP and CD31. For details, see article by Zhang and colleagues on page 5198.