

BREAKING ADVANCES

- 1201 | **Highlights from Recent Cancer Literature**

REVIEWS

- 1203 | **Pten in the Breast Tumor Microenvironment: Modeling Tumor–Stroma Coevolution**
Julie A. Wallace, Fu Li, Gustavo Leone, and Michael C. Ostrowski
- 1208 | **Small Molecule Inhibitors Targeting the "Achilles' Heel" of Androgen Receptor Activity**
Marianne D. Sadar

PERSPECTIVE

- 1214 | **Significance and Mechanism of Lymph Node Metastasis in Cancer Progression**
Kenji Kawada and Makoto M. Taketo

PRIORITY REPORTS

- 1219 | **Tumor Suppressor RARRES1 Interacts with Cytoplasmic Carboxypeptidase AGBL2 to Regulate the α -Tubulin Tyrosination Cycle**
Ziad J. Sahab, Michael D. Hall, You Me Sung, Sivanesan Dakshanamurthy, Yun Ji, Deepak Kumar, and Stephen W. Byers
- Précis:* This study identifies a long sought tubulin tyrosine carboxypeptidase and its tumor suppressor inhibitor with important implications for microtubule-targeted cancer therapeutics.

- 1229 | **Recovery of Anoikis in Src-Transformed Cells and Human Breast Carcinoma Cells by Restoration of the SIRP α 1/SHP-2 Signaling System**
Kazuo Hara, Takeshi Senga, Md. Helal Uddin Biswas, Hitoki Hasegawa, Satoko Ito, Toshinori Hyodo, Yoshiaki Hirooka, Yasumasa Niwa, Hidemi Goto, and Michinari Hamaguchi

Précis: Findings offer an important advance in understanding the control of anoikis, an adhesion deprivation-induced form of apoptosis that is generally important in cancer biology.

MICROENVIRONMENT AND IMMUNOLOGY

- 1235 | **B7-H1 Overexpression Regulates Epithelial–Mesenchymal Transition and Accelerates Carcinogenesis in Skin**
Yujia Cao, Lu Zhang, Yosuke Kamimura, Patcharee Ritprajak, Masaaki Hashiguchi, Sachiko Hirose, and Miyuki Azuma

Précis: An immune cell regulatory molecule implicated in immune escape is often overexpressed in solid tumor cells, where it also promotes epithelial-mesenchymal transition, hinting at intriguing links between these two hallmarks of cancer progression.

- 1244 | **HIF-1 α Confers Aggressive Malignant Traits on Human Tumor Cells Independent of Its Canonical Transcriptional Function**
Young-Gun Yoo, Jared Christensen, and L. Eric Huang

Précis: HIF-1 α exerts a critical role in malignant progression through a novel pathway characterized in this study, potentially explaining the common overexpression of HIF-1 α in aggressive cancers.

- 1253 | **Antigen Spreading Contributes to MAGE Vaccination-Induced Regression of Melanoma Metastases**
Véronique Corbière, Jacques Chapiro, Vincent Stroobant, Wenbin Ma, Christophe Lurquin, Bernard Lethé, Nicolas van Baren, Benoît J. Van den Eynde, Thierry Boon, and Pierre G. Coulie

Précis: Findings promote understanding of how cancer vaccines can trigger tumor rejection responses in humans.

1263 **Clinical Impact of Different Classes of Infiltrating T Cytotoxic and Helper Cells (Th1, Th2, Treg, Th17) in Patients with Colorectal Cancer**
Marie Tosolini, Amos Kirilovsky, Bernhard Mlecnik, Tessa Fredriksen, Stéphanie Mauger, Gabriela Bindea, Anne Berger, Patrick Bruneval, Wolf-Herman Fridman, Franck Pagès, and Jérôme Galon

Précis: Results define roles for T-cell subpopulations that infiltrate human colorectal cancers, offering opportunities to improve clinical prognosis and treatment decisions.

1272 **Altered TGF- β Signaling in a Subpopulation of Human Stromal Cells Promotes Prostatic Carcinogenesis**
Omar E. Franco, Ming Jiang, Douglas W. Strand, James Peacock, Suzanne Fernandez, Roger S. Jackson II, Monica P. Revelo, Neil A. Bhowmick, and Simon W. Hayward

Précis: Interactions between stromal fibroblasts with different capacities to respond to TGF- β contribute to a microenvironment which can promote malignant progression.

1302 **MTGR1 Is Required for Tumorigenesis in the Murine AOM/DSS Colitis-Associated Carcinoma Model**
Caitlyn W. Barrett, Barbara Fingleton, Amanda Williams, Wei Ning, Melissa A. Fischer, Mary K. Washington, Rupesh Chaturvedi, Keith T. Wilson, Scott W. Hiebert, and Christopher S. Williams

Précis: Findings connect a transcriptional repressor of the AML/ETO family involved in leukemia to a requirement for efficient inflammatory carcinogenesis in the colon.

1313 **miR-99 Family of MicroRNAs Suppresses the Expression of Prostate-Specific Antigen and Prostate Cancer Cell Proliferation**
Dandan Sun, Yong Sun Lee, Ankit Malhotra, Hak Kyun Kim, Mirela Matecic, Clive Evans, Roderick V. Jensen, Christopher A. Moskaluk, and Anindya Dutta

Précis: A family of microRNAs with tumor suppressor function in prostate cancer targets a master class of regulators of chromatin organization and cell growth that regulate the prognostic factor prostate-specific antigen.

1325 **Activation of NF- κ B by TMPRSS2/ERG Fusion Isoforms through Toll-Like Receptor-4**
Jianghua Wang, Yi Cai, Long-jiang Shao, Javed Siddiqui, Nallasivam Palanisamy, Rile Li, Chengxi Ren, Gustavo Ayala, and Michael Ittmann

Précis: Findings suggest that Toll receptor signaling to NF- κ B during tissue infection or inflammation may drive progression of premalignant prostatic lesions and prostate cancers that involve the commonly activated fusion oncogene TMPRSS2/ERG.

1334 **Raf Kinase Inhibitor Protein RKIP Enhances Signaling by Glycogen Synthase Kinase-3 β**
Fahd Al-Mulla, Milad S. Bitar, May Al-Maghrebi, Abdulla I. Behbehani, Waleed Al-Ali, Oliver Rath, Brendan Doyle, Kit Yee Tan, Andrew Pitt, and Walter Kolch

Précis: Important mechanistic findings reveal the RKIP/GSK3 signaling axis as a potential therapeutic target for addressing cancer progression.

MOLECULAR AND CELLULAR PATHOBIOLOGY

1282 **PIPK1 γ Regulates β -Catenin Transcriptional Activity Downstream of Growth Factor Receptor Signaling**
Mark Schramp, Narendra Thapa, Jessica Heck, and Richard Anderson

Précis: Findings identify a phosphoinositide-generating enzyme as a direct trigger for nuclear translocation of β -catenin, which promotes a central pathway of oncogenic gene expression and tumorigenesis.

1292 **Forkhead Transcription Factor Foxq1 Promotes Epithelial-Mesenchymal Transition and Breast Cancer Metastasis**
Haijun Zhang, Fanyan Meng, Gang Liu, Bin Zhang, Jun Zhu, Feng Wu, Stephen P. Ethier, Fred Miller, and Guojun Wu

Précis: This important study reveals an essential intermediary transcription factor linking TGF β 1 signaling to E-cadherin control in regulation of the epithelial-mesenchyme transition, a critical determinant of the metastatic potential in many types of carcinoma.

1344

Replication and Functional Genomic Analyses of the Breast Cancer Susceptibility Locus at 6q25.1 Generalize Its Importance in Women of Chinese, Japanese, and European Ancestry

Qiuyin Cai, Wanqing Wen, Shimian Qu, Guoliang Li, Kathleen M. Egan, Kexin Chen, Sandra L. Deming, Hongbing Shen, Chen-Yang Shen, Marilie D. Gammon, William J. Blot, Keitaro Matsuo, Christopher A. Haiman, Ui Soon Khoo, Motoki Iwasaki, Regina M. Santella, Lina Zhang, Alecia Malin Fair, Zhibin Hu, Pei-Ei Wu, Lisa B. Signorello, Linda Titus-Ernstoff, Kazuo Tajima, Brian E. Henderson, Kelvin Y.K. Chan, Yoshio Kasuga, Polly A. Newcomb, Hong Zheng, Yong Cui, Furu Wang, Ya-Lan Shieh, Hiroji Iwata, Loic Le Marchand, Sum Yin Chan, Martha J. Shrubsole, Amy Trentham-Dietz, Shoichiro Tsugane, Montserrat Garcia-Closas, Jirong Long, Chun Li, Jiajun Shi, Bo Huang, Yong-Bing Xiang, Yu-Tang Gao, Wei Lu, Xiao-Ou Shu, and Wei Zheng

Précis: Results from this large consortium study broaden the significance of a chromosomal marker associated with breast cancer risk in women of diverse ancestry.

1356

Genome-Wide Significant Association Between a Sequence Variant at 15q15.2 and Lung Cancer Risk

Thorunn Rafnar, Patrick Sulem, Soren Besenbacher, Daniel F. Gudbjartsson, Carlo Zanon, Julius Gudmundsson, Simon N. Stacey, Jelena P. Kostic, Thorgeir E. Thorgeirsson, Gudmar Thorleifsson, Hjordis Bjarnason, Halla Skuladottir, Tomas Gudbjartsson, Helgi J. Isaksson, Dolores Isla, Laura Murillo, Maria D. Garcia-Prats, Angeles Panadero, Katja K.H. Aben, Sita H. Vermeulen, Henricus F.M. van der Heijden, William J. Feser, York E. Miller, Paul A. Bunn, Augustine Kong, Holly J. Wolf, Wilbur A. Franklin, Jose I. Mayordomo, Lambertus A. Kiemeny, Steinn Jonsson, Unnur Thorsteinsdottir, and Kari Stefansson

Précis: Findings identify a lung cancer risk variant of genome-wide significance that is independent of smoking quantity and distinct from TP53BP1 coding variants.

1362

Targeting Activin Receptor-Like Kinase 1 Inhibits Angiogenesis and Tumorigenesis through a Mechanism of Action Complementary to Anti-VEGF Therapies

Dana D. Hu-Lowe, Enhong Chen, Lianglin Zhang, Katherine D. Watson, Patrizia Mancuso, Patrick Lappin, Grant Wickman, Jeffrey H. Chen, Jianying Wang, Xin Jiang, Karin Amundson, Ronald Simon, Andreas Erbersdobler, Simon Bergqvist, Zheng Feng, Terri A. Swanson, Brett H. Simmons, John Lippincott, Gerald F. Casperson, Wendy J. Levin, Corrado Gallo Stampino, David R. Shalinsky, Katherine W. Ferrara, Walter Fiedler, and Francesco Bertolini

Précis: Findings offer mechanistic and pharmacologic information that significantly advances understanding of the biology and therapeutic utility of ALK1 antibodies for cancer treatment.

1374

Therapeutic Antibody Targeting of CD47 Eliminates Human Acute Lymphoblastic Leukemia

Mark P. Chao, Ash A. Alizadeh, Chad Tang, Max Jan, Rachel Weissman-Tsukamoto, Feifei Zhao, Christopher Y. Park, Irving L. Weissman, and Ravindra Majeti

Précis: CD47 is an independent prognostic factor and represents a novel therapeutic antibody target for the treatment of human acute lymphoblastic leukemia.

1385

Small Molecule Kinase Inhibitor Screen Identifies Polo-Like Kinase 1 as a Target for Neuroblastoma Tumor-Initiating Cells

Natalie Grinshtein, Alessandro Datti, Mayumi Fujitani, David Uehling, Michael Prakesch, Methvin Isaac, Meredith S. Irwin, Jeffrey L. Wrana, Rima Al-awar, and David R. Kaplan

Précis: Findings identify kinases that regulate growth and survival of neuroblastoma tumor-initiating cells, highlighting PLK1 as an attractive therapeutic target for treating advanced neuroblastoma.

1396 **E-3810 Is a Potent Dual Inhibitor of VEGFR and FGFR that Exerts Antitumor Activity in Multiple Preclinical Models**
Ezia Bello, Gennaro Colella, Valentina Scarlato, Paolo Oliva, Alexander Berndt, Giovanni Valbusa, Sonia Colombo Serra, Maurizio D'Incalci, Ennio Cavalletti, Raffaella Giavazzi, Giovanna Damia, and Gabriella Camboni

Précis: Extensive preclinical study of a novel dual-targeted small molecule inhibitor of VEGF and FGF receptors reveal striking antiangiogenic and antitumor effects that warrant clinical evaluation.

1406 **Molecular Mechanism of MART-1⁺/A*0201⁺ Human Melanoma Resistance to Specific CTL-Killing Despite Functional Tumor-CTL Interaction**
Ali R. Jazirehi, Stavroula Baritaki, Richard C. Koya, Benjamin Bonavida, and James S. Economou

Précis: Alterations in antiapoptotic cell signaling dynamics, rather than loss of peptide and/or MHC complex, represent the major mechanism by which melanomas escape tumor-specific T cells.

1418 **Targeting RNA Polymerase I with an Oral Small Molecule CX-5461 Inhibits Ribosomal RNA Synthesis and Solid Tumor Growth**
Denis Drygin, Amy Lin, Josh Bliesath, Caroline B. Ho, Sean E. O'Brien, Chris Proffitt, Mayuko Omori, Mustapha Haddach, Michael K. Schwabe, Adam Siddiqui-Jain, Nicole Streiner, Jaclyn E. Quin, Elaine Sanij, Megan J. Bywater, Ross D. Hannan, David Ryckman, Kenna Anderes, and William G. Rice

Précis: This study offers preclinical proof-of-concept that drug-like small molecule inhibitors of RNA polymerase I could offer a widely applicable strategy to treat human cancer.

1431 **Noncytotoxic Differentiation Treatment of Renal Cell Cancer**
Soledad Negrotto, Zhenbo Hu, Oscar Alcazar, Kwok Peng Ng, Pierre Triozzi, Daniel Lindner, Brian Rini, and Yogen Saunthararajah

Précis: Noncytotoxic mesenchymal to epithelial differentiation therapy for renal cell cancer is a mechanistically distinct therapeutic approach with potentially unique advantages.

1442 **The Metastasis-Associated microRNA miR-516a-3p Is a Novel Therapeutic Target for Inhibiting Peritoneal Dissemination of Human Scirrhous Gastric Cancer**
Yoshifumi Takei, Misato Takigahira, Keichiro Mihara, Yuzo Tarumi, and Kazuyoshi Yanagihara

Précis: An antimetastatic microRNA is defined with an initial preclinical proof-of-concept for its possible use in blocking dissemination of metastatic gastric cancers.

1454 **Polymalic Acid-Based Nanobiopolymer Provides Efficient Systemic Breast Cancer Treatment by Inhibiting both HER2/neu Receptor Synthesis and Activity**
Satoshi Inoue, Hui Ding, Jose Portilla-Arias, Jinwei Hu, Bindu Konda, Manabu Fujita, Andres Espinoza, Sonal Suhane, Marisa Riley, Marcus Gates, Rameshwar Patil, Manuel L. Penichet, Alexander V. Ljubimov, Keith L. Black, Eggehard Holler, and Julia Y. Ljubimova

Précis: This preclinical study illustrates how combining multiple genetic and antibody targeting principles into a single nanobiopolymer system can provide an effective strategy to treat cancer.

1465 **Fes Tyrosine Kinase Expression in the Tumor Niche Correlates with Enhanced Tumor Growth, Angiogenesis, Circulating Tumor Cells, Metastasis, and Infiltrating Macrophages**
Shengnan Zhang, Violeta Chitu, E. Richard Stanley, Bruce E. Elliott, and Peter A. Greer

Précis: Findings offer an in vivo genetic proof that Fes provides an essential support to breast cancer growth and metastasis through action in vascular endothelial and myeloid cells in the tumor microenvironment.

TUMOR AND STEM CELL BIOLOGY

1474 **VEGFR-1 Expressed by Malignant Melanoma-Initiating Cells Is Required for Tumor Growth**
Natasha Y. Frank, Tobias Schatton, Soo Kim, Qian Zhan, Brian J. Wilson, Jie Ma, Karim R. Saab, Veronika Oshero, Hans R. Widlund, Martin Gasser, Ana-Maria Waaga-Gasser, Thomas S. Kupper, George F. Murphy, and Markus H. Frank

Précis: Vascular mimicry, a mechanism evolved by melanomas as a strategy to gain a blood supply, is regulated by melanoma stem-like cells that express the well established angiogenic receptor VEGFR-1.

1486

Activation of the Androgen Receptor by Intratumoral Bioconversion of Androstanediol to Dihydrotestosterone in Prostate Cancer

James L. Mohler, Mark A. Titus, Suxia Bai, Brian J. Kennerley, Fred B. Lih, Kenneth B. Tomer, and Elizabeth M. Wilson

Précis: Findings suggest how the androgen receptor may continue to drive prostate cancer growth in patients treated with androgen deprivation therapy, despite low circulating levels of testicular androgens, with implications for therapeutic improvements.

1497

Fusion between Intestinal Epithelial Cells and Macrophages in a Cancer Context Results in Nuclear Reprogramming

Anne E. Powell, Eric C. Anderson, Paige S. Davies, Alain D. Silk, Carl Pelz, Soren Impey, and Melissa H. Wong

Précis: Transcriptome changes in epithelial/macrophage cell fusion hybrids that can occur in cancer may provide a pathophysiological foundation for metastatic progression.

CORRECTIONS

1506

Correction: Gadd45a Functions As a Promoter or Suppressor of Breast Cancer Dependent on the Oncogenic Stress

1507

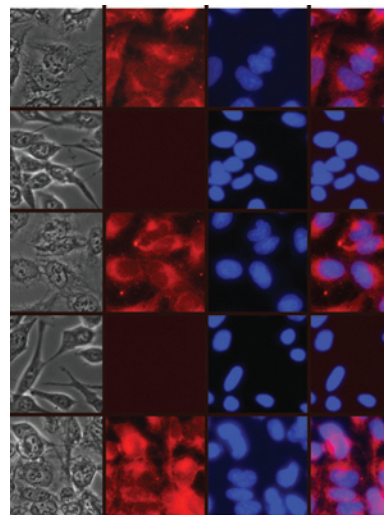
Correction: Dual Functional Monoclonal Antibody PF-04605412 Targets Integrin $\alpha 5 \beta 1$ and Elicits Potent Antibody-Dependent Cellular Cytotoxicity

1508

Correction: Transcriptional Control of the *ERBB2* Amplicon by *ERR α* and *PGC-1 β* Promotes Mammary Gland Tumorigenesis

ABOUT THE COVER

The hypoxia-inducible factor 1 α (HIF-1 α) has long been recognized as a key transcription factor to mediate hypoxic effects on tumor growth and progression. By inactivating the canonical function of HIF-1 α transcriptional activity, the study by Yoo and colleagues demonstrates that HIF-1 α promotes malignant progression via a novel HIF- α -c-Myc pathway of genetic alteration to confer various malignant traits, including epithelial-mesenchymal transition as shown by immunofluorescent staining of E-cadherin (red). Although transduced U-2 OS cells expressing a stabilized HIF-1 α lost E-cadherin (2nd row), inactivation of the HIF-1 α -c-Myc pathway (3rd row) but not the HIF-1 α transcriptional activity (4th row) obliterated HIF-1 α -induced epithelial-mesenchymal transition. For details, see the article by Yoo and colleagues on page 1244 of this issue.



Cancer Research

The Journal of Cancer Research (1916–1930) | The American Journal of Cancer (1931–1940)

71 (4)

Cancer Res 2011;71:1201-1508.

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