

BREAKING ADVANCES

- 1883 **Highlights from Recent Cancer Literature**


REVIEWS

- 1885 **Obesity and Cancer: A Gut Microbial Connection**
Naoko Ohtani, Shin Yoshimoto, and Eiji Hara
- 1890 **Transforming Growth Factor- β as a Therapeutic Target in Hepatocellular Carcinoma**
 Gianluigi Giannelli, Erica Villa, and Michael Lahn

PRIORITY REPORT

- 1895 **A Common Cancer-Associated DNA Polymerase ϵ Mutation Causes an Exceptionally Strong Mutator Phenotype, Indicating Fidelity Defects Distinct from Loss of Proofreading**
Daniel P. Kane and Polina V. Shcherbakova
- Précis:** This study describes the functional consequences of the most frequent DNA polymerase variant linked to colorectal and endometrial cancer, challenging the recently forwarded idea that hypermutated human cancers must result from loss of exonucleolytic proofreading.

INTEGRATED SYSTEMS AND TECHNOLOGIES

- 1902 **Noninvasive Quantification of Solid Tumor Microstructure Using VERDICT MRI**
 Eletheria Panagiotaki, Simon Walker-Samuel, Bernard Siow, S. Peter Johnson, Vineeth Rajkumar, R. Barbara Pedley, Mark F. Lythgoe, and Daniel C. Alexander
- Précis:** This article highlights the superior qualities of a novel noninvasive imaging method to monitor tumor development and therapeutic response in preclinical models.
- 1913 **Apoptosis Imaging for Monitoring DR5 Antibody Accumulation and Pharmacodynamics in Brain Tumors Noninvasively**
Thomas G. Weber, Franz Osl, Anja Renner, Thomas Pöschinger, Stefanie Galbán, Alnawaz Rehemtulla, and Werner Scheuer
- Précis:** This preclinical study reports a method to quantify antibody accumulation and pharmacodynamics in brain tumors, where delivery after systemic administration is often difficult to assess, offering a holistic in vivo approach to assess CNS-targeting drugs.

MICROENVIRONMENT AND IMMUNOLOGY

- 1924 **VISTA Is an Immune Checkpoint Molecule for Human T Cells**
J. Louise Lines, Eirini Pantazi, Justin Mak, Lorenzo F. Sempere, Li Wang, Samuel O'Connell, Sabrina Ceeraz, Arief A. Suriawinata, Shaofeng Yan, Marc S. Ernstoff, and Randolph Noelle
- Précis:** Therapeutic inactivation of CTLA-4-related molecules like VISTA may have enormous potential for generalized immunotherapy of cancer.
- 1933 **VISTA Regulates the Development of Protective Antitumor Immunity**
Isabelle Le Mercier, Wenna Chen, Janet L. Lines, Maria Day, Jiannan Li, Petra Sargent, Randolph J. Noelle, and Li Wang
- Précis:** This study offers a preclinical proof-of-concept to evaluate the efficacy and mechanisms of action of a VISTA-targeting antibody in multiple tumor models.
- 1945 **Vaccine-Mediated Immunotherapy Directed against a Transcription Factor Driving the Metastatic Process**
Andressa Ardiani, Sofia R. Gameiro, Claudia Palena, Duane H. Hamilton, Anna Kwilas, Thomas H. King, Jeffrey Schlom, and James W. Hodge
- Précis:** This study offers a preclinical proof-of-concept for an antimetastasis vaccine targeting Twist, a transcription factor that promotes metastasis and drug resistance in many tumor types.
- 1958 **T Lymphocytes Restrain Spontaneous Metastases in Permanent Dormancy**
Irene Romero, Cristina Garrido, Ignacio Algarra, Antonia Collado, Federico Garrido, and Angel M. Garcia-Lora
- Précis:** This study describes a preclinical model for dormant metastases controlled by the immune system, an understanding of which may lead to new insights into how to extend survival by blocking relapses of metastatic cancer.
- 1969 **IL-17A Produced by $\gamma\delta$ T Cells Promotes Tumor Growth in Hepatocellular Carcinoma**
Shoubao Ma, Qiao Cheng, Yifeng Cai, Huanle Gong, Yan Wu, Xiao Yu, Liyun Shi, Depei Wu, Chen Dong, and Haiyan Liu
- Précis:** These findings offer new insights into how the pro-inflammatory cytokine IL-17A influences tumor immunity, with potential implications for the development of tumor immunotherapy.

Table of Contents

MOLECULAR AND CELLULAR PATHOBIOLOGY

- 1983** **β -Catenin Inhibitor ICAT Modulates the Invasive Motility of Melanoma Cells**
Mélanie J. Domingues, Florian Rambow, Bastien Job, Laura Papon, Wanguo Liu, Lionel Larue, and Jacky Bonaventure
Précis: ICAT inhibition reduces the mesenchymal-amoeboid transition involved in invasive cancer cell motility, limiting metastasis formation.
- 1996** **Src Kinase Is a Novel Therapeutic Target in Lymphangioleiomyomatosis**
Alexey Tyryshkin, Abhisek Bhattacharya, and N. Tony Eissa
Précis: This study provides a mechanistic rationale to immediately reposition the use of Src inhibitors currently in clinical trials for the treatment of malignancies associated with mutation of the tumor suppressor gene TSC2.
- 2006** **PP2A-B55 β Antagonizes Cyclin E1 Proteolysis and Promotes Its Dysregulation in Cancer**
YingMeei Tan, Dahui Sun, Weijian Jiang, Kathleen Klotz-Noack, Ajay A. Vashisht, James Wohlschlegel, Martin Widschwendter, and Charles Spruck
Précis: As a candidate therapeutic target, overexpressed cyclin E1 is a driving force of hormone-independent growth, genetic instability, and progression of "triple-negative" breast cancers and other aggressive cancers.
- 2015** **LRH-1 Governs Vital Transcriptional Programs in Endocrine-Sensitive and -Resistant Breast Cancer Cells**
Stéphanie Bianco, Mylène Brunelle, Maïka Jangal, Luca Magnani, and Nicolas Gévry
Précis: This study shows how the nuclear receptor LRH-1 modulates the sensitivity of breast cancer cells to antiestrogen therapy, suggesting new insights into how resistance may emerge to limit treatment effectiveness.
- 2026** **Latency-Associated Nuclear Antigen of Kaposi Sarcoma-Associated Herpesvirus Promotes Angiogenesis through Targeting Notch Signaling Effector Hey1**
Xing Wang, Zhiheng He, Tian Xia, Xiaofan Li, Deguang Liang, Xianzhi Lin, Hao Wen, and Ke Lan
Précis: These findings identify a therapeutic target for treatment of Kaposi sarcoma, a cancer best known for its association with AIDS patients at highest risk of this herpesvirus-driven disease.

- 2038** **Tumor-Infiltrating Myeloid Cells Activate Dll4/Notch/TGF- β Signaling to Drive Malignant Progression**
Hidetaka Ohnuki, Kan Jiang, Dunrui Wang, Ombretta Salvucci, Hyeonil Kwak, David Sánchez-Martin, Dragan Maric, and Giovanna Tosato
Précis: This study describes a myeloid cell-carcinoma signaling network that links the tumor microenvironment in new ways with tumor growth, highlighting opportunities to target tumors where this network is active.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

- 2050** **CBP Loss Cooperates with PTEN Haploinsufficiency to Drive Prostate Cancer: Implications for Epigenetic Therapy**
Liya Ding, Shuai Chen, Ping Liu, Yunqian Pan, Jian Zhong, Kevin M. Regan, Ligu Wang, Chunrong Yu, Anthony Rizzardi, Liang Cheng, Jun Zhang, Stephen C. Schmechel, John C. Chevillat, Jan Van Deursen, Donald J. Tindall, and Haojie Huang
Précis: These results suggest new insights into prostate cancer etiology, establishing a central role for histone modification and providing a rationale for clinical evaluation of epigenetic-targeted therapy in prostate cancer patients.
- 2062** **Novel Mechanistic Insights into Ectodomain Shedding of EGFR Ligands Amphiregulin and TGF- α : Impact on Gastrointestinal Cancers Driven by Secondary Bile Acids**
Nagaraj S. Nagathihalli, Yugandhar Beesetty, Woojin Lee, M. Kay Washington, Xi Chen, A. Craig Lockhart, and Nipun B. Merchant
Précis: These findings define an EGF-related signaling pathway that mediates the oncogenic effects of secondary bile acids in gastrointestinal cancers, the targeting of which may enhance therapeutic responses.
- 2073** **Bioluminescent Imaging of HPV-Positive Oral Tumor Growth and Its Response to Image-Guided Radiotherapy**
Rong Zhong, Matt Pytynia, Charles Pelizzari, and Michael Spiotto
Précis: More rapid visualization of HPV-positive oral tumor growth will assist the development of chemotherapeutic and radiotherapeutic strategies to stem this rapidly growing disease.

Table of Contents

TUMOR AND STEM CELL BIOLOGY

- 2082** **Small GTPase RhoE/Rnd3 Is a Critical Regulator of Notch1 Signaling**
Zehua Zhu, Kristina Todorova, Kevin K. Lee, Jun Wang, Eunjeong Kwon, Ivan Kehayov, Hyung-Gu Kim, Vihren Kolev, G. Paolo Dotto, Sam W. Lee, and Anna Mandinova

Précis: These findings describe an important regulatory feedback on a key tumor suppressor pathway that may have a pivotal role in epithelial tumors.

- 2094** **Attenuation of microRNA-126 Expression That Drives CD34⁺38⁻ Stem/Progenitor Cells in Acute Myeloid Leukemia Leads to Tumor Eradication**

David C. de Leeuw, Fedor Denkers, Marjolein C. Olthof, Arjo P. Rutten, Walter Pouwels, Gerrit Jan Schuurhuis, Gert J. Ossenkoppele, and Linda Smit

Précis: These findings define miR-126 as a therapeutic focus to specifically eradicate stem-like cells in acute myeloid leukemias that tend to relapse in patients despite early positive responses to chemotherapy.

- 2106** **NOTCH3 Signaling Regulates MUSASHI-1 Expression in Metastatic Colorectal Cancer Cells**

Anna Pastò, Valentina Serafin, Giorgia Pilotto, Claudia Lago, Chiara Bellio, Livio Trusolino, Andrea Bertotti, Timothy Hoey, Michelina Plateroti, Giovanni Esposito, Marica Pinazza, Marco Agostini, Donato Nitti, Alberto Amadori, and Stefano Indraccolo

Précis: These findings point to a specific inhibition of NOTCH2/3, rather than NOTCH1, as a strategy for attacking cancer stem-like cells in metastatic colon cancer.

- 2119** **shRNA Kinome Screen Identifies TBK1 as a Therapeutic Target for HER2⁺ Breast Cancer**

Tao Deng, Jeff C. Liu, Philip E.D. Chung, David Uehling, Ahmed Aman, Babu Joseph, Troy Ketela, Zhe Jiang, Nathan F. Schachter, Robert Rottapel, Sean E. Egan, Rima Al-awar, Jason Moffat, and Eldad Zacksenhaus

Précis: These results identify a novel target to improve treatment of HER2-positive breast cancer through leveraging existing anti-HER2 therapy.

CORRECTION

- 2131** **Correction: Epithelial Junction Opener JO-1 Improves Monoclonal Antibody Therapy of Cancer**

 AC icon indicates Author Choice

For more information please visit www.aacrjournals.org

ABOUT THE COVER

Numerous reports have now demonstrated that the epithelial-to-mesenchymal transition (EMT) process is involved in solid tumor progression, metastases, and drug resistance. Several transcription factors have been implicated as drivers of EMT and metastatic progression, including Twist, which has been shown to be associated with poor prognosis and drug resistance for many carcinomas and other tumor types. The role of a Twist vaccine in experimental cancer metastases has been principally studied in the 4T1 mammary tumor model, where there is a greater than 3-fold increase in Twist expression in lung metastases (shown) vs. the primary tumor. Vaccination of mice reduced the size of primary transplanted 4T1 tumors and had an even greater antitumor effect on lung metastases of the same mice, which was dependent on Twist-specific T cells. These studies provide the rationale for vaccine-induced T-cell-mediated therapy of transcription factors involved in driving the metastatic process. For details, see article by Ardiani and colleagues on page 1945.

