# Cancer Research

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### REVIEWS

1885  
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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**  

**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, Erini Pantazi, Justin Mak, Lorenzo F. Sempere, Li Wang, Samuel O’Connell, Sabrina Ceeraz, Ariel A. Suriavinata, 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 Sergent, 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 Ardiian, Sofia R. Gameiro, Claudia Palena, Duane H. Hamilton, Anna Kwi, Thomas H. King, Jeffrey Schom, and James W. Hodge

**Précis:** This study offers a preclinical proof-of-concept for an ant metastasis 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. García-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 γδ 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.
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-B55β Antagonizes Cyclin E1 Proteolysis and Promotes Its Dysregulation in Cancer
YingMeei Tan, Dahuai Sun, Weijian Jiang, Kathleen Klotz-Noack, Ajay A. Vashishth, 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 Blanco, Mylène Brunelle, Maïka Jangal, Luca Magnani, and Nicolas Gévy

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, Zhicheng 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-β1 Signaling to Drive Malignant Progression
Hidetaka Ohnuki, Kan Jiang, Dunrui Wang, Ombretta Salvucci, Hyeongil Kwak, David Sánchez-Martín, Dragan Maric, and Giovanna Tosato

Précis: This study describes a myeloid cell–cancer signaling network that links the tumor microenvironment in new ways with tumor growth, highlighting opportunities to target tumors where this network is active.

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, Liguo Wang, Chunrong Yu, Anthony Rizzardi, Liang Cheng, Jun Zhang, Stephen C. Schmechel, John C. Cheville, 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, Wooin 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.
Small GTPase RhoE/Rnd3 Is a Critical Regulator of Notch1 Signaling

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

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

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

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.