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 Poschinger, Stefanie Galbán, Almawaz Rehemtulla, and Werner Scheuер

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, Eririni Pantazi, Justin Mak, Lorenzo F. Sempere, Li Wang, Samuel O’Connell, Sabrina Ceeraz, Arielf Suriavintna, 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 Ardiani, Sofia R. Gameiro, Claudia Palena, Duane H. Hamilton, Anna Kwilas, Thomas H. King, Jeffrey Schom, and James W. Hodge

Précis: This study offers a preclinical proof-of-concept for an antimitastasis 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, Dahui Sun, Weijian Jiang, Kathleen Klotz-Noack, Ajay A. Vashish, James Wohlschlegel, Martin Widschwendter, and Charles Spruck

Précis: As a candidate therapeutic target, overexpressed cyclin E1 is driving a 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, Mylene 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.
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.

Attenuation of microRNA-126 Expression That Drives CD34⁺/CD38⁻ 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.

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

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.