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Breaking Advances

2131 Highlights from Recent Cancer Literature

Reviews

2133 DNA Damage in Cancer Therapeutics: A Boon or a Curse?
Anchit Khanna

2139 Classifying Cancers Based on T-cell Infiltration and PD-L1
Michele W.L. Teng, Shin Foong Ngioow, Antoni Ribas, and Mark J. Smyth

Priority Reports

2146 Therapeutically Targetable ALK Mutations in Leukemia
Précis: These findings suggest a rationale for personalized treatment of certain leukemia patients with ALK kinase inhibitors, with immediate implications for clinical evaluation.

2151 Tumor-Induced Pressure in the Bone Microenvironment Causes Osteocytes to Promote the Growth of Prostate Cancer Bone Metastases
Joseph L. Sottnik, Jinlu Dai, Honglai Zhang, Brittany Campbell, and Evan T. Keller
Précis: This study illuminates the critical contribution of physical forces to tumor cell growth in the tumor microenvironment, identifying osteocytes as critical mediators of the effect of this force in the bone metastatic niche.

2159 Mechanistic Rationale to Target PTEN-Deficient Tumor Cells with Inhibitors of the DNA Damage Response Kinase ATM
Nuala McCabe, Conor Hanna, Steven M. Walker, David Gonda, Jie Li, Katarina Wikstrom, Kieran I. Savage, Karl T. Butterworth, Clark Chen, D. Paul Harkin, Kevin M. Prise, and Richard D. Kennedy
Précis: These results offer a preclinical mechanistic rationale for clinical evaluation of ATM inhibitors for treatment of PTEN-deficient tumors.

Microenvironment and Immunology

2166 Effective Eradication of Glioblastoma Stem Cells by Local Application of an AC133/CD133-Specific T-cell–Engaging Antibody and CD8 T Cells
Shruti Prasad, Simone Gaedicke, Marcia Machen, Gerhard Mittler, Friederike Braun, Michael Hettich, Elke Firat, Kerstin Klingner, Julia Schuler, Dagmar Wider, Ralph M. Wäsch, Christel Herold-Mende, Ursula Ekässer-Beile, and Gabriele Niedermann
Précis: In combination with a T-cell microinfusion into the brain, a novel bispecific antibody that delivers T cells to glioma stem-like cells mediates strong antitumor effects.

2177 Full-Length Semaphorin-3C Is an Inhibitor of Tumor Lymphangiogenesis and Metastasis
Yelena Mumblat, Ofra Kessler, Neta Ilan, and Gera Neufeld
Précis: An antibody-based strategy to block the development of new lymph vessels into tumors, as well as the metastasis of tumor cells into lymph nodes, suggests the antibody may offer generalized therapeutic potential to treat any solid tumor.

2187 JAK Inhibition Impairs NK Cell Function in Myeloproliferative Neoplasms
Kathrin Schönberg, Janna Rudolph, Maria Vonnahme, Sowmya Parampillai Vijanarayana, Isabelle Comez, Maryam Hejazi, Angela R. Manser, Markus Uhrberg, Walter Verbeek, Steffen Koschmieder, Tim H. Brummendorf, Peter Brossart, Annkristin Heine, and Dominik Wolf
Précis: Findings indicate that the approved JAK kinase inhibitor Jakafi (Incyte) significantly depletes natural killer cells in patients, possibly explaining the higher rates of infection reported with drug treatment in either approved or experimental settings where this drug is being tested.

2200 CTLA-4+ Regulatory T Cells Increased in Cetuximab-Treated Head and Neck Cancer Patients Suppress NK Cell Cytotoxicity and Correlate with Poor Prognosis
Précis: These findings suggest that the response to anti-EGFR therapy could be improved by the addition of anti-CTLA-4 therapy, with immediate implications for clinical translation.
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## 2211
**Decreased Ferroportin Promotes Myeloma Cell Growth and Osteoclast Differentiation**
Zhimin Gu, He Wang, Jiliang Xia, Ye Yang, Zhendong Jin, Hongwei Xu, Jimei Shi, Ivana De Domenico, Guido Tricot, and Fenghuang Zhan

*Précis:* Components of pathways that regulate iron metabolism are being identified as increasingly appealing therapeutic targets for cancer treatment in a variety of settings.

## 2222
**Microenvironmental Remodeling as a Parameter and Prognostic Factor of Heterogeneous Leukemogenesis in Acute Myelogenous Leukemia**
Jin-A Kim, Jae-Seung Shim, Ga-Young Lee, Hyeon Woo Yim, Tae-Min Kim, Myungshin Kim, Sun-Hee Leem, Jong-Wook Lee, Chang-Ki Min, and Il-Hoan Oh

*Précis:* These results demonstrate that the bone marrow microenvironment of leukemia patients at initial diagnosis could be used to predict high risk of leukemic relapse for management of leukemic disease.

## 2232
**TGFβ Is a Master Regulator of Radiation Therapy-Induced Antitumor Immunity**
Claire Vanpouille-Box, Julie M. Diamond, Karsten A. Pilones, Jiri Zavadil, James S. Babb, Silvia C. Formenti, Mary Helen Barcellos-Hoff, and Sandra Demaria

*Précis:* Patients who receive local radiotherapy can benefit from cotreatment with a neutralizing TGFβ antibody, which appears to generate a personalized vaccination effect against the tumor, even in patients who do not respond to immune checkpoint blockade.

### MOLECULAR AND CELLULAR PATHOBIOLOGY

#### 2243
**Combined Label-Free Quantitative Proteomics and microRNA Expression Analysis of Breast Cancer Unravel Molecular Differences with Clinical Implications**
Angelo Gámez-Pozo, Julia Berges-Soria, Jorge M. Arevalillo, Paolo Narini, Rocio López-Vacas, Hilario Navarro, Jonas Grossmann, Carlos A. Castaneda, Paloma Main, Mariana Díaz-Almirón, Enrique Espinosa, Eva Ciruelos, and Juan Ángel Fresno Vara

*Précis:* The integration of different levels of information, such as those provided by proteomics and microRNA expression analysis, offers a means to study the biologic outcome of cancer-related genomic abnormalities, thus providing biologic insights as well as a wave of novel candidate biomarkers and therapeutic targets.

## 2254
**Hepcidin Regulation in Prostate and Its Disruption in Prostate Cancer**

*Précis:* These findings show how secretion of an iron-regulatory hormone originally thought to be synthesized exclusively in liver promotes prostate cancer cell survival, providing a new link between iron metabolism and prostate cancer.

## 2264
**Development of Lung Adenocarcinomas with Exclusive Dependence on Oncogenic Fusions**
Motonobu Saito, Yoko Shimada, Kouya Shiraiishi, Hiromi Sakamoto, Koji Tsuta, Hirohiko Totsuka, Suemori Chiku, Hitoshi Ichikawa, Mamoru Kato, Shun-ichi Watanabe, Teruhiko Yoshida, Jun Yokota, and Takashi Kohn

*Précis:* Fusion-positive LADC cases are characterized by dramatically fewer mutations in TP53 and other cancer-related genes than other types of LADCs, supporting the current therapeutic use of tyrosine kinase inhibitors targeting specific fusion products in fusion-positive cases.

### THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

#### 2272
**Rho Kinase Inhibitors Block Melanoma Cell Migration and Inhibit Metastasis**
Amine Sadok, Ashan McCarthy, John Caldwell, Ian Collins, Michelle D. Garrett, Maggie Yeo, Steven Hooper, Erik Salahi, Sandra Kuenmer, Faraz K. Mardakheh, and Christopher J. Marshall

*Précis:* This study offers a preclinical proof of concept of the therapeutic potential of novel effective inhibitors of the Rho GTPase effector kinases ROCK1/2.

#### 2285
**Optimizing a Lupus Autoantibody for Targeted Cancer Therapy**
Philip W. Noble, Grace Chan, Melissa R. Young, Richard H. Weisbart, and James E. Hansen

*Précis:* These findings offer a preclinical proof of principle for the use of an optimized nuclear-penetrating autoantibody against DNA as a targeted therapy for tumors with preexisting defects in homology-directed repair.
ABOUT THE COVER

Some lupus autoantibodies penetrate into live cells, and the potential to use these cell-penetrating antibodies against cancer is an emerging concept. An optimized lupus anti-DNA antibody construct, 3E10 di-scFv, has now been shown to localize into cell nuclei and to selectively cause accumulation of DNA damage in and kill cancer cells with certain defects in DNA repair and therefore has potential in targeted cancer therapy. In this image the fluorescent signal demonstrates nuclear localization by the optimized lupus antibody construct in DLD1 colon cancer cells that were immunostained after treatment with 3E10 di-scFv. For details, see article by Noble and colleagues on page 2285.