

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 Ngiew, Antoni Ribas, and Mark J. Smyth

PRIORITY REPORTS

- 2146** Therapeutically Targetable ALK Mutations in Leukemia
Julia E. Maxson, Monika A. Davare, Samuel B. Luty, Christopher A. Eide, Bill H. Chang, Marc M. Loriaux, Cristina E. Tognon, Daniel Bottomly, Beth Wilmot, Shannon K. McWeeney, Brian J. Druker, and Jeffrey W. Tyner
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, Kienan 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
Shruthi Prasad, Simone Gaedicke, Marcia Machein, Gerhard Mittler, Friederike Braun, Michael Hettich, Elke Firat, Kerstin Klingner, Julia Schüler, Dagmar Wider, Ralph M. Wäsch, Christel Herold-Mende, Ursula Elsässer-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 Parampalli Yajnanarayana, Isabelle Cornez, 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
Hyun-Bae Jie, Patrick J. Schuler, Steve C. Lee, Raghvendra M. Srivastava, Athanassios Argiris, Soldano Ferrone, Theresa L. Whiteside, and Robert L. Ferris
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, Jumei 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** **TGF β Is a Master Regulator of Radiation Therapy-Induced Antitumor Immunity**

Claire Vanpouille-Box, Julie M. Diamond, Karsten A. Pilonis, 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 TGF β 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 Nanni, Rocío 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**

Lia Tesfay, Kathryn A. Clausen, Jin Woo Kim, Poornima Hegde, Xiaohong Wang, Lance D. Miller, Zhiyong Deng, Nicole Blanchette, Tara Arvedson, Cindy K. Miranti, Jodie L. Babbitt, Herbert Y. Lin, Donna M. Peehl, Frank M. Torti, and Suzy V. Torti

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 Oncogene Fusions**



Motonobu Saito, Yoko Shimada, Kouya Shiraishi, Hiromi Sakamoto, Koji Tsuta, Hirohiko Totsuka, Suenori Chiku, Hitoshi Ichikawa, Mamoru Kato, Shun-ichi Watanabe, Teruhiko Yoshida, Jun Yokota, and Takashi Kohno

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, Afshan McCarthy, John Caldwell, Ian Collins, Michelle D. Garrett, Maggie Yeo, Steven Hooper, Erik Sahai, Sandra Kuemper, 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.

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- 2292** **Ormeloxifene Suppresses Desmoplasia and Enhances Sensitivity of Gemcitabine in Pancreatic Cancer**
 Sheema Khan, Mara C. Ebeling, Neeraj Chauhan, Paul A. Thompson, Rishi K. Gara, Aditya Ganju, Murali M. Yallapu, Stephen W. Behrman, Haotian Zhao, Nadeem Zafar, Man Mohan Singh, Meena Jaggi, and Subhash C. Chauhan
Précis: Combining gemcitabine with a nonsteroidal drug that targets stromal tissue might improve therapeutic outcomes in pancreatic cancer, based on the preclinical proof of concept provided in this study

- 2305** **Pancreatic Cancer Combination Therapy Using a BH3 Mimetic and a Synthetic Tetracycline**
 Bridget A. Quinn, Rupesh Dash, Siddik Sarkar, Belal Azab, Praveen Bhoopathi, Swadesh K. Das, Luni Emdad, Jun Wei, Maurizio Pellecchia, Devanand Sarkar, and Paul B. Fisher
Précis: These findings offer preclinical proof of concept for a combination therapy that exhibits robust efficacy in multiple models of pancreatic cancer, with immediate implications for clinical evaluation.

- 2316** **Silencing $\beta 3$ Integrin by Targeted ECO/siRNA Nanoparticles Inhibits EMT and Metastasis of Triple-Negative Breast Cancer**
 Jenny G. Parvani, Maneesh D. Gujrati, Margaret A. Mack, William P. Schiemann, and Zheng-Rong Lu
Précis: Integrins in cancer cells offer intriguing targets for drug therapy, but effective systemic methods to ablate their function or expression as a strategy to block metastatic disease have been elusive.

TUMOR AND STEM CELL BIOLOGY

- 2326** **miR-25 Modulates Invasiveness and Dissemination of Human Prostate Cancer Cells via Regulation of α_v - and α_6 -Integrin Expression**
 E. Zoni, G. van der Horst, A.F. van de Merbel, L. Chen, J.K. Rane, R.C.M. Pelger, A.T. Collins, T. Visakorpi, B.E. Snaar-Jagalska, N.J. Maitland, and G. van der Pluijm
Précis: This mechanistic advance in understanding the invasive behavior of metastasis-initiating stem-like cells in prostate cancer, the first step in progression to untreatable disease, suggests a new targeted approach to eradicate this important tumor cell subpopulation.

- 2337** **FoxM1 Drives a Feed-Forward STAT3-Activation Signaling Loop That Promotes the Self-Renewal and Tumorigenicity of Glioblastoma Stem-like Cells**
 Ai-hua Gong, Ping Wei, Sicong Zhang, Jun Yao, Ying Yuan, Ai-dong Zhou, Frederick F. Lang, Amy B. Heimberger, Ganesh Rao, and Suyun Huang
Précis: These findings define how the key glioma-driving growth factor PDGF-A is upregulated in glioma and define a transcriptional network required to maintain self-renewal of stem-like cells in this deadly brain cancer.

- 2349** **Vimentin-ERK Signaling Uncouples Slug Gene Regulatory Function**
 Reetta Virtakoivu, Anja Mai, Elina Mattila, Nicola De Franceschi, Susumu Y. Imanishi, Garry Corthals, Riina Kaukonen, Markku Saari, Fang Cheng, Elin Torvaldson, Veli-Matti Kosma, Arto Mannermaa, Ghaffar Muharram, Christine Gilles, John Eriksson, Ylermi Soini, James B. Lorens, and Johanna Ivaska
Précis: These findings identify a pivotal step in controlling the ability of the transcription factor Slug to organize hallmarks of EMT, a key driver of metastasis.

- 2363** **PLK1 and HOTAIR Accelerate Proteasomal Degradation of SUZ12 and ZNF198 during Hepatitis B Virus-Induced Liver Carcinogenesis**
 Hao Zhang, Ahmed Diab, Huitao Fan, Saravana Kumar Kailasam Mani, Ronald Hullinger, Philippe Merle, and Ourania Andrisani
Précis: Upregulation of the mitotic kinase Plk1 and the noncoding RNA HOTAIR deregulates chromatin-modifying complexes, which elicit gene expression changes broadly linked to malignant development.

- 2375** **Leptin-STAT3-G9a Signaling Promotes Obesity-Mediated Breast Cancer Progression**
 Chao-Ching Chang, Meng-Ju Wu, Jer-Yen Yang, Ignacio G. Camarillo, and Chun-Ju Chang
Précis: These results define an epigenetic program that controls cancer stem-like cell plasticity during obesity-related breast cancer progression, suggesting a novel therapeutic paradigm to suppress stem-like cell pools and limit breast malignancy.

- 2387** **SOC2 Controls Proliferation and Stemness of Hematopoietic Cells under Stress Conditions and Its Deregulation Marks Unfavorable Acute Leukemias**
 Caterina Vitali, Claudia Bassani, Claudia Chiodoni, Elisa Fellini, Carla Guarnotta, Silvia Miotti, Sabina Sangaletti, Fabio Fuligni, Loris De Cecco, Pier P. Piccaluga, Mario P. Colombo, and Claudio Tripodo
Précis: These findings illuminate how hematopoietic stemness is maintained during development and progression of aggressive blood tumors.

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LETTER TO THE EDITOR

- 2400** Drug Combination Studies and Their Synergy Quantification Using the Chou–Talalay Method—Letter
John C. Ashton

CORRECTION

- 2401** Correction: HOXB7, a Homeodomain Protein, Is Overexpressed in Breast Cancer and Confers Epithelial–Mesenchymal Transition

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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.

