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
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, 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
Shruthi Prasad, Simone Gaedicke, Marcia Machin, Gerhard Mittler, Friederike Braun, Michael Hettich, Elke Firat, Kerstin Klingner, Julia Schuler, Dagmar Wider, Ralph M. Wäsch, Christel Herold-Mende, Ursula Eckser-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 Parampilli 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
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.
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.

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.

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.

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. Arevillillo, 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.

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.

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.

Rho Kinase Inhibitors Block Melanoma Cell Migration and Inhibit Metastasis
Anne Sadok, Ashan 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.

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.
Ormeloxifene Suppresses Desmoplasia and Enhances Sensitivity of Gemcitabine in Pancreatic Cancer
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.

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.

Silencing β3 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

miR-25 Modulates Invasiveness and Dissemination of Human Prostate Cancer Cells via Regulation of αv- and α5-integrin Expression
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 subgroup.

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, Sichong 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.

Vimentin–ERK Signaling Uncouples Slug Gene Regulatory Function
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.

PLK1 and HOTAIR Accelerate Proteasomal Degradation of SUZ12 and ZNF198 during Hepatitis B Virus–Induced Liver Carcinogenesis
Hao Zhang, Ahmed Diab, Hui Tao 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.

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.

SOCS2 Controls Proliferation and Stemness of Hematopoietic Cells under Stress Conditions and Its Deregression Marks Unfavorable Acute Leukemias
Caterina Vitali, Claudia Bassani, Claudia Chiodoni, Elisa Fellini, Carla Guarnotta, Silvia Miotti, Sabina Sangaletti, Fabio Fulligni, 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.
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

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.