BREAKING ADVANCES

1243  Highlights from Recent Cancer Literature

REVIEWS

1245  Interplay between Immune Checkpoint Proteins and Cellular Metabolism
Sangbin Lim, Joshua B. Phillips, Luciana Madeira da Silva, Ming Zhou, Oystein Fodstad, Laurie B. Owen, and Ming Tan

1250  Recommended Guidelines for Validation, Quality Control, and Reporting of TP53 Variants in Clinical Practice

INTEGRATED SYSTEMS AND TECHNOLOGIES

1271  Systematic Pan-Cancer Analysis Reveals Immune Cell Interactions in the Tumor Microenvironment
Frederick S. Varn, Yue Wang, David W. Mullins, Steven Fiering, and Chao Cheng

MICROENVIRONMENT AND IMMUNOLOGY

1283  Bone Pain Induced by Multiple Myeloma Is Reduced by Targeting V-ATPase and ASIC3
Masahiro Hiasa, Tatsuo Okui, Yohance M. Allett, Matthew S. Ripsch, Ge-Hong Sun-Wada, Hiroki Wakabayashi, G. David Roodman, Fletcher A. White, and Toshiyuki Yoneda
Précis: These findings present a mechanistic rationale to relieve the severe bone pain experienced by multiple myeloma patients, with immediate clinical implications for treatment.

1296  A Multifunctional Role for Adjuvant Anti-4-1BB Therapy in Augmenting Antitumor Response by Chimeric Antigen Receptor T Cells
Précis: Combination therapy using an agonistic antibody can significantly enhance CAR T-cell response, concomitant with reduced numbers of immunosuppressive cell types, suggesting a potentially powerful approach to treat solid cancers with adoptive immunotherapy.

1310  Radiation-Induced Enhancement of Antitumor T-cell Immunity by VEGF-Targeted 4-1BB Costimulation
Brett Schrand, Bhavna Verma, Agata Levy, Shradha Patel, Iris Castro, Ana Paula Benaduce, Randall Brenneman, Oliver Umland, Hideo Yagita, Eli Gilboa, and Adrian Ishkanian
Précis: Immunomodulatory aptamers can be targeted directly to tumors by binding to radiation-induced tumor stress products, increasing therapeutic index.

1322  Immune Toxicities Elicited by CTLA-4 Blockade in Cancer Patients Are Associated with Early Diversification of the T-cell Repertoire
David Y. Oh, Jason Cham, Li Zhang, Serena S. Kwek, Mark Klinger, Malek Faham, and Lawrence Fong
Précis: Autoimmune side effects often seen with immune checkpoint inhibitors are associated with rapid increases in the diversity of the circulating T-cell pool.
Tumor-Associated Neutrophils and Macrophages Promote Gender Disparity in Hepatocellular Carcinoma in Zebrafish
Chuan Yan, Qi Ji Yang, and Zhiyuan Gong
Précis: Increased production of the chronic inflammation factor cortisol contributes to the predominance of liver cancer development in males versus females.

Biomarker Dynamics in B-cell Lymphoma: A Longitudinal Prospective Study of Plasma Samples Up to 25 Years before Diagnosis
Florentin Späth, Carl Wilbom, Esmeralda J.M. Kroep, Ann-Sofie Johansson, Ingegar A. Bergdahl, Roel Vermeulen, and Beatrice Melin
Précis: Sustained B-cell activation is a dynamic process during lymphomagenesis that may be indicative of occult disease or disease progression in monitoring patients with indolent lymphomas.

Reprogramming Medulloblastoma-Propagating Cells by a Combined Antagonism of Sonic Hedgehog and CXCR4
Stacey A. Ward, Nicole M. Warrington, Sara Taylor, Najla Kfouri, Ingejin Luo, and Joshua B. Rubin
Précis: These findings suggest a mechanism-based approach to eradicate the most recalcitrant cells in one common type of pediatric brain cancer.

Constitutive NOTCH3 Signaling Promotes the Growth of Basal Breast Cancers
Lisa Choy, Thiis J. Hagenbeek, Margaret Solon, Dorothy French, David Finkle, Amy Shelton, Dorothy French, David Finkle, Amy Shelton, Rayna Venook, Matthew J. Brauer, and Christian W. Siebel
Précis: An antibody that can directly assess receptor signaling distinguishes constitutive and ligand-independent activity of the oncogenic Notch pathway in enabling the malignant growth of basal breast cancers.
1453 Bone Marrow Adipocytes Facilitate Fatty Acid Oxidation Activating AMPK and a Transcriptional Network Supporting Survival of Acute Monocytic Leukemia Cells

Précis: These findings suggest that targeting metabolic abnormalities in leukemia cells located in the bone marrow is potentially promising and innovative therapeutic approach.

1465 Fibrinolytic Enzyme Cotherapy Improves Tumor Perfusion and Therapeutic Efficacy of Anticancer Nanomedicine
Ameya R. Kirtane, Tanmoy Sadhukha, Hyunjoon Kim, Vidhi Khanna, Brenda Koniar, and Jayanth Panyam

Précis: These findings suggest that cotherapy with a fibrinolytic enzyme could be used to improve diffusion, intratumoral distribution, and overall effectiveness of anticancer nanomedicine.

1476 [18F](2S,4R)4-Fluoroglutamine PET Detects Glutamine Pool Size Changes in Triple-Negative Breast Cancer in Response to Glutaminase Inhibition
Rong Zhou, Austin R. Pantel, Shihong Li, Brian P. Lieberman, Karl Ploesel, Hoon Choi, Eric Blankemeyer, Hsiaoju Lee, Hank F. Kung, Robert H. Mach, and David A. Mankoff

Précis: These findings reveal the utility of a noninvasive PET imaging method to monitor pharmacodynamic responses to cancer drugs that target glutamine breakdown.

1485 Prostate Cancer Patients with Late Radiation Toxicity Exhibit Reduced Expression of Genes Involved in DNA Double-Strand Break Repair and Homologous Recombination
Bregje van Oorschot, Lon Uitterhoeve, Ilja Oomen, Rosemarie ten Cate, Ian Paul Medema, Harry Vieling, Lukas J.A. Stalpers, Perry D. Moerland, and Nicolaas A.P. Franken

Précis: Patients who are inherently less efficient at DNA double-strand break repair may be at risk for severe late radiation toxicity.

1492 Aberrant SYK Kinase Signaling Is Essential for Tumorigenesis Induced by TSC2 Inactivation
Ye Cui, Wendy K. Steagall, Anthony M. Lamattina, Gustavo Pacheco-Rodriguez, Mario Stylianou, Pranav Kidambi, Benjamin Stump, Fernanda Golzarri, Ivan O. Rosas, Carmen Priolo, Elizabeth P. Henske, Joel Moss, and Souheil El-Chemaly

Précis: These results illuminate how mutations in the tumor suppressor gene TSC2 lead to formation of a variety of organ lesions.

CORRECTIONS
1503 Correction: Long Noncoding RNA GCASPC, a Target of miR-17-3p, Negatively Regulates Pyruvate Carboxylase-Dependent Cell Proliferation in Gallbladder Cancer

1504 Correction: Cdk5 Directly Targets Nuclear p21CIP1 and Promotes Cancer Cell Growth

1505 Correction: Differential Regulation of the Melanoma Proteome by eIF4A1 and eIF4E

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ABOUT THE COVER

Many human tumors are characterized by extensive fibrin deposition in their extracellular matrix. Shown here is a representative image of a human colon tumor section stained for fibrin. For details, see article by Kirtane and colleagues on page 1465.