BREAKING ADVANCES

6135 Highlights from Recent Cancer Literature

CANCER RESEARCH 75TH ANNIVERSARY COMMENTARIES

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Irwin H. Gelman

6140 KIT Oncogenic Mutations: Biologic Insights, Therapeutic Advances, and Future Directions
Jonathan A. Fletcher

6143 Commentary on microRNA Fingerprint in Human Epithelial Ovarian Cancer
Marilena V. Iorio and Carlo M. Croce

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6146 Metabolite and Microbiome Interplay in Cancer Immunotherapy
Caroline H. Johnson, Mary E. Spilker, Laura Goetz, Scott N. Peterson, and Gary Siuzdak

6153 Humanized Mouse Xenograft Models: Narrowing the Tumor–Microenvironment Gap
J. Jason Morton, Gregory Bird, Yosef Refaeli, and Antonio Jimeno

PERSPECTIVES

6159 Connecting (T)issues: How Research in Fascia Biology Can Impact Integrative Oncology
Helene M. Langevin, Patricia Keely, Jun Mao, Lisa M. Hodge, Robert Schleip, Gary Deng, Boris Hinz, Melody A. Swartz, Beverley A. de Valois, Suzanna Zick, and Thomas Findley

6163 PET and MRI: Is the Whole Greater than the Sum of Its Parts?
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INTEGRATED SYSTEMS AND TECHNOLOGIES

6171 EpCAM-Regulated Transcription Exerts Influences on Nanomechanical Properties of Endometrial Cancer Cells That Promote Epithelial-to-Mesenchymal Transition
Ya-Ting Hsu, Pawel Osmulski, Yao Wang, Yi-Wen Huang, Lu Liu, Jianhua Ruan, Victor X. Jin, Nameer B. Kirma, Maria E. Gaczynska, and Tim Hui-Ming Huang
Précis: This study advances understanding of how the biophysical properties of cancer cells must be altered to achieve an epithelial-mesenchyme transition in their status, a pivotal step in gaining invasive properties that can elude normal tissue barriers.

MICROENVIRONMENT AND IMMUNOLOGY

6183 BPTF Depletion Enhances T-cell–Mediated Antitumor Immunity
Kimberly Mayes, Suehyb G. Alkhaitib, Kristen Peterson, Aiman Alhazmi, Carolyn Song, Vivian Chan, Tana Blevins, Mark Roberts, Catherine I. Dumur, Xiang-Yang Wang, and Joseph W. Landry
Précis: The results of this study document a novel chromatin regulator, which, when inhibited, improves antitumor immunity.

6193 Nutritional Stress Induced by Tryptophan-Degrading Enzymes Results in ATF4-Dependent Reprogramming of the Amino Acid Transporter Profile in Tumor Cells
Elina Timosenko, Hemza Ghadbane, Jonathan D. Silk, Dawn Shepherd, Uzi Gileadi, Lauren J. Howson, Robert Laynes, Qi Zhao, Robert L. Strausberg, Lars R. Olsen, Stephen Taylor, Francesca M. Buffa, Richard Boyd, and Vincenzo Cerundolo
Précis: These findings reveal the mechanisms by which cancer cells but not T cells can compensate for tryptophan deprivation in a tumor microenvironment by upregulating the expression of amino acid transporters that mediate cellular tryptophan uptake.
6205  Snail1-Dependent Activation of Cancer-Associated Fibroblast Controls Epithelial Tumor Cell Invasion and Metastasis
Lorena Alba-Castellón, Rubén Olivera-Salgueiro, Aida Mestre-Farrara, Raül Peña, Mercedes Herrera, Félix Bonilla, J. Ignacio Casal, Josep Baulida, Cristina Peña, and Antonio García de Herreros

Précis: Eliminating Snail1 function in tumor stromal fibroblasts prevent the invasive capacity of epithelial tumor cells.

6218  Interleukin-30 Promotes Breast Cancer Growth and Progression
Irma Airolid, Claudia Cocco, Carlo Sorrentino, Domenico Angelucci, Serena Di Meo, Lamberto Manzoli, Laura Iezzi, Clara Natoli, and Emma Di Carlo

Précis: This study describes the breast cancer-promoting activity of endogenous IL30 in the tumor microenvironment, which promotes tumor cell proliferation, migration, and inflammatory characters associated with a metastatic program, with potential biomarker and therapeutic implications.

6230  Ccl22 Diverts T Regulatory Cells and Controls the Growth of Melanoma
Jared Klarquist, Kristen Tobin, Peyman Farhangi Oskuei, Steven W. Henning, Manuel F. Fernandez, Emilia R. Dellaceca, Flor C. Navarro, Jonathan M. Eby, Shilpak Chatterjee, Shikhar Mehrotra, Joseph I. Clark, and I. Caroline Le Poole

Précis: These findings offer preclinical proof of concept for the potential utility of the chemokine CCL22, as delivered by local injection, to enhance the efficacious response of immune checkpoint therapy in melanoma patients while suppressing the autoimmune side-effects of the treatment.

6241  Thymic Stromal Chemokine TSLP Acts through Th2 Cytokine Production to Induce Cutaneous T-cell Lymphoma
Naomi Takahashi, Makoto Sugaya, Hiraku Suga, Tomonori Oka, Makiko Kawaguchi, Tomomitsu Miyagaki, Hideki Fujita, and Shinichir Sato

Précis: A growth-reinforcing cycle reported in atopic dermatitis also functions in cutaneous T-cell lymphoma, not only inducing a Th2-dominant tumor environment but also stimulating tumor cell proliferation in this malignancy.

6253  Trametinib Drives T-cell–Dependent Control of KRAS-Mutated Tumors by Inhibiting Pathological Myelopoiesis

Précis: This study reveals a new perspective on the antitumor activity of FDA-approved MEK inhibitors, revealing that they enhance protective immunity in vivo by influencing multiple cell types in divergent ways, acting overall to prevent the accumulation of immunosuppressive leukocytes in tumor beds.

6266  Agonistic CD40 mAb-Driven IL12 Reverses Resistance to Anti-PD1 in a T-cell-Rich Tumor
Shin Foong Ngiow, Arabella Young, Stephen I. Blake, Geoffrey R. Hill, Hideo Yagita, Michele W.L. Teng, Alan J. Korman, and Mark J. Smyth

Précis: This study offers a proof-of-concept framework to systematically identify immune conditioning agents that can convert PD1hi T cells to PD1lo T cells, with clinical implications for the management of patients resistant to anti-PD1 immune checkpoint antibodies.

MOLLEcular AND CELLULAR PATHOBIOLOGY

6278  Wnt Signaling Promotes Breast Cancer by Blocking ITCH-Mediated Degradation of YAP/TAZ Transcriptional Coactivator WBP2
Shen Kiat Lim, Ssu Yi Lu, Shin-He Kang, Hock Jin Tan, Zilin Li, Zhen Ning Adrian Woe, Iye Swei Guan, Vishnu Priyanka Reddy Chichili, J. Savaraman, Thomas Putti, Aye Aye Thike, Puay Hoon Tan, Marius Sudol, David M. Virshup, Siew Wee Chan, Wanjin Hong, and Yoon Pin Lim

Précis: This study identifies how a new oncogene in breast cancer is normally suppressed to prevent aberrant growth but becomes activated to promote cancer, with potential implications to understand and therapeutically exploit a critical interface between the WNT and Hippo signaling pathways that drive this disease.

6290  MNX1 Is Oncogenically Upregulated in African-American Prostate Cancer
Li Zhang, Jianghua Wang, Yongquan Wang, Yiqun Zhang, Patricia Castro, Longjiang Shao, Arun Sreekumar, Nagireddy Putluri, Nilanjan Guha, Saligram Deepak, Arunkumar Padmanaban, Chad J. Creighton, and Michael Ittmann

Précis: An oncogene regulated by androgen and AKT is activated in prostate cancers relatively more frequently in African-American men, potentially offering a novel therapeutic target to address the increased incidence of aggressive disease in this patient population.
Preclinical Efficacy of the Auristatin-Based BET Inhibitors Suppress ALDH Activity by LncRNA HOXA11-AS Promotes Proliferation and Invasion of Gastric Cancer by Scaffolding the Chromatin Modification Factors PRC2, LSD1, and DNMT1

Precis: New therapeutic directions are suggested by this mechanistic study of a gastric cancer-associated long noncoding RNA, which coordinates tumor suppressor functions.

Posttranscriptional Uregulation of p53 by Reactive Oxygen Species in Chronic Lymphocytic Leukemia

Precis: These findings suggest that reactivation of the full transcriptional activities of p53 in proliferating chronic lymphocytic leukemia may offer a possible therapeutic strategy.

BET Inhibitors Suppress ALDH Activity by Targeting ALDH1A1 Super-Enhancer in Ovarian Cancer

Precis: BET inhibitors offer a novel strategy to target ALDH activity, a functional marker in cancer stem-like cells, which in combination with platinum-based therapies are shown to have efficacious effects in ovarian cancer.

Preclinical Efficacy of the Auristatin-Based Antibody–Drug Conjugate BAY 1187982 for the Treatment of FGFR2-Positive Solid Tumors

Precis: These findings offer preclinical proof of concept for a candidate small-molecule therapy that can increase the efficacy of radiotherapy without increasing apparent side effects.

Ovarian Cancer Chemoresistance Relies on the Stem Cell Reprogramming Factor PBX1

These findings offer a mechanistic rationale to target the PBX1/STAT3 axis in ovarian cancers to defeat a key mechanism of chemoresistance, which emerges in nearly every patient after first-line treatment.

Histone H3K27 Trimethylation Modulates the Chromatin Modification Factors PRC2, and LSD1, and DNMT1

Precis: These findings establish a rationale to pursue high-throughput meta-analysis of liver cancer patient specimens to develop and target common and subtype-specific cancer networks.

Impaired Planar Germ Cell Division in the Testis, Caused by Dissociation of RHAMM from the Spindle, Results in Hypofertility and Seminoma

Precis: These findings identify the spindle-associated protein RHAMM as an intrinsic regulator of male germ cell fate and as a gatekeeper preventing initiation of testicular germ cell tumors.

Ovarian Cancer Chemoresistance Relies on the Stem Cell Reprogramming Factor PBX1

Precis: These findings suggest new biomarkers with potential clinical utility to identify patients who could benefit most from aggressive adjuvant chemotherapy.

Integrative Genomic Analysis Identifies the Core Transcriptional Hallmarks of Human Hepatocellular Carcinoma

Precis: These findings establish a rationale to pursue high-throughput meta-analysis of liver cancer patient specimens to develop and target common and subtype-specific cancer networks.
6396  EGFL6 Regulates the Asymmetric Division, Maintenance, and Metastasis of ALDH⁺ Ovarian Cancer Cells
Shoumei Bai, Patrick Ingram, Yu-Chih Chen, Ning Deng, Alex Pearson, Yashar S. Niknafs, Patrick O'Hayer, Yun Wang, Zhong-Yin Zhang, Elisa Boscolo, Joyce Bischoff, Euisik Yoon, and Ronald J. Buckanovich
Précis: These results offer preclinical proof of concept for a compelling new therapeutic target to improve the management of ovarian cancer.

6410  TG2 and NF-κB Signaling Coordinates the Survival of Mantle Cell Lymphoma Cells via IL6-Mediated Autophagy
Han Zhang, Zheng Chen, Roberto N. Miranda, L. Jeffrey Medeiros, and Nami McCarty
Précis: These results illuminate a novel interconnected network of signaling and autophagy pathways in a clinically problematic form of non-Hodgkin lymphoma, the disruption of which may offer an effective therapeutic strategy.

6424  Ablation of miR-10b Suppresses Oncogene-Induced Mammary Tumorigenesis and Metastasis and Reactivates Tumor-Suppressive Pathways
Jongchan Kim, Ashley N. Siverly, Dahu Chen, Min Wang, Yuan Yuan, Yumeng Wang, Hyemin Lee, Jinsong Zhang, William J. Muller, Han Liang, Boyi Gan, Xianbin Yang, Yutong Sun, M. James You, and Li Ma
Précis: These results establish the critical function of an oncomiR that drives metastasis, termed a metastamiR, and define the set of critical tumor suppressor mechanisms it overcomes to drive breast cancer progression.

CORRECTION
6436  Correction: miR-29b Mediates NF-κB Signaling in KRAS-Induced Non–Small Cell Lung Cancers

ABOUT THE COVER
Upregulation of the stem cell reprogramming factor PBX1 mediates resistance to platinum-based chemotherapy in ovarian cancer. Using an in vitro dual-color competition assay, PBX1-positive cells were labeled green and PBX1-negative cells were labeled red. It was found that PBX1-positive cells escaped the cytotoxic effects from a platinum-based agent, carboplatin, much more efficiently than did PBX1-negative cells, as demonstrated by an increased green to red ratio at several days following carboplatin treatment. For details, see article by Jung and colleagues on page 6351.