BREAKING ADVANCES

987  Highlights from Recent Cancer Literature

CANCER RESEARCH 75TH ANNIVERSARY

COMMENTARIES

989  Commentary on Eagle and Foley: "Cytotoxicity in Human Cell Cultures"
    Michael B. Sporn

991  Commentary on Sandberg et al., "The In Vivo Chromosome Constitution of Marrow"
    Bayard D. Clarkson

REVIEW

994  At the Crossroads of Cancer Stem Cells, Radiation Biology, and Radiation Oncology
    Leo E. Gerweck and Hiroaki Wakimoto

PRIORITY REPORT

999  STK11/LKB1 Deficiency Promotes Neutrophil Recruitment and Proinflammatory Cytokine Production to Suppress T-cell Activity in the Lung Tumor Microenvironment
    Précis: These findings illustrate how loss-of-function mutation of a tumor suppressor can contribute to the generation of an immunosuppressive tumor microenvironment, a feature of tumor suppressor loss that may emerge as one of its most important consequences.

INTEGRATED SYSTEMS AND TECHNOLOGIES

1009  Abscopal Benefits of Localized Radiotherapy Depend on Activated T-cell Trafficking and Distribution between Metastatic Lesions
    Jan T. Poleszczuk, Kimberly A. Luddy, Sotiris Prokopiou, Mark Robertson-Tessi, Eduardo G. Moros, Mayer Fishman, Julie Y. Djeu, Steven E. Finkelstein, and Heiko Enderling
    Précis: A basis to predict which metastatic lesions in a patient may be able to trigger systemic immune-mediated regressions after localized radiotherapy—a phenomenon known as the abscopal effect—has the potential to radically improve outcomes, including in the context of immune checkpoint treatments currently being tested in combination in radiotherapy.

MICROENVIRONMENT AND IMMUNOLOGY

1019  HSPB1 Inhibits the Endothelial-to-Mesenchymal Transition to Suppress Pulmonary Fibrosis and Lung Tumorigenesis
    Seo-Hyun Choi, Jae-Kyung Nam, Bu-Yeo Kim, Junho Jang, Young-Bae Jin, Hae-June Lee, Seungwoo Park, Young Hoon Ji, Jae-Ho Cho, and Yoon-Jin Lee
    Précis: These findings identify an endothelial heat shock protein as a key regulator of the endothelial-to-mesenchymal transition in pulmonary fibrosis and lung cancer, with implications for the development of new therapeutics to treat fibrotic diseases.

1031  Identification of the Cell-Intrinsic and -Extrinsic Pathways Downstream of EGFR and IFNγ That Induce PD-L1 Expression in Head and Neck Cancer
    Fernando Concha-Benavente, Raghvendra M. Srivastava, Sumita Trivedi, Yu Lei, Uma Chandran, Raja R. Seethala, Gordon J. Freeman, and Robert L. Ferris
    Précis: These findings elucidate the mechanisms underlying upregulation of PD-L1 in head and neck cancer and suggest that treatment with JAK inhibitors might offer an indirect strategy to block PD-L1–mediated immune checkpoint signaling in this setting.
MOLECULAR AND CELLULAR
PATHOBIOLOGY

1044 Novel Morphologic and Genetic Analysis of Cancer Cells in a 3D Microenvironment Identifies STAT3 as a Regulator of Tumor Permeability Barrier Function
Min Chul Park, Hyobin Jeong, Sung Hwa Son, YounHa Kim, Daeyoung Han, Peter C. Goughnour, Tahee Kang, Nam Hoon Kwon, Hyo Eun Moon, Sun Ha Paek, Daehye Hwang, Ho Jun Seol, Do-Hyun Nam, and Sunghoon Kim

Précis: Among its many cancer-promoting roles, STAT3 also appears to act as a pivotal modifier function in supporting the poor permeability of tumors to anticancer drugs, reinforcing interest in its targeting to treat advanced drug-resistant cancers.

1055 An Immune-Inflammation Gene Expression Signature in Prostate Tumors of Smokers

Précis: These findings suggest that tissue inflammation and nicotine-induced molecular alterations can accelerate the development of prostate tumors in smokers, offering an explanation for why they tend to exhibit relatively faster disease progression.

1066 Photodynamic Therapy Synergizes with Irinotecan to Overcome Compensatory Mechanisms and Improve Treatment Outcomes in Pancreatic Cancer
Huang-Chiao Huang, Srivalleesha Mallidi, Joyce Liu, Chun-Te Chiang, Zhiming Mai, Ruth Goldschmidt, Neema Ebrahim-Zadeh, Imran Rizvi, and Tayyaba Hasan

Précis: These findings offer a preclinical proof of concept showing how cooperative therapies that overcome compensatory growth pathways in pancreatic cancer can improve its clinical management.

1078 DNA-PKcs and PARP1 Bind to Unresected Stalled DNA Replication Forks Where They Recruit XRCC1 to Mediate Repair
Songmin Ying, Zihuai Chen, Annette L. Medhurst, Jessica A. Neal, Zhengqiang Bao, Oliver L. Medhurst, Joanna McGourtan, Xinming Song, Huazhao Shen, Freddie C. Hamdy, Benedikt M. Kessler, Kathryn Meek, and Thomas Helleday

Précis: DNA lesions and stalled replication forks are resolved through common cellular repair mechanisms, with important implications for understanding how genomic integrity is lost in cancer cells as a result of accumulated replication stress.

1089 Bidirectional Notch Signaling and Osteocyte-Derived Factors in the Bone Marrow Microenvironment Promote Tumor Cell Proliferation and Bone Destruction in Multiple Myeloma

Précis: These findings illustrate how osteocytes in the multiple myeloma microenvironment promote malignant growth and associated bone diseases, with implications for new points of intervention to eradicate this subset of tumor-supportive bone marrow stromal cells.

1101 miR-892b Silencing Activates NF-κB and Promotes Aggressiveness in Breast Cancer
Lili Jiang, Liang Yu, Xin Zhang, Fangyong Lei, Lan Wang, Xiangxia Liu, Shu Wu, Jinrong Zhu, Geyan Wu, Linxue Cao, Aibin Liu, Libing Song, and Jun Li

Précis: Aberrant microRNA silencing underlies constitutively activated NF-κB signaling in breast cancer, encouraging the development of therapeutic mimics of tumor suppressor microRNAs that can attenuate oncogenic pathways.

1112 SOX4 Is Essential for Prostate Tumorigenesis Initiated by PTEN Ablation
Birdal Bilir, Adeboye O. Osunkoya, W. Guy Wiles IV, Soma Sannigrahi, Veronique Lefebvre, Daniel Metzger, Demetri D. Spyropoulos, W. David Martin, and Carlos S. Moreno

Précis: This study offers preclinical proof of concept for targeting SOX4 pathways in prostate cancers and other types of cancers, where this transcription factor is commonly overexpressed and where it provides an intersection of well-established oncogenic signaling axes in human malignancy.
The CDK9 Inhibitor Dinaciclib Exerts Potent Antiangiogenic and Antitumor Effects in Preclinical Models of MLL-Rearranged Acute Myeloid Leukemia


Précis: Acute myeloid leukemias harboring MLL translocations are typically refractory to conventional chemotherapy, but they appear to respond potently to CDK inhibitors, with near-term implications for clinical evaluation.

PREVENTION AND EPIDEMIOLOGY

Herbacetin Is a Novel Allosteric Inhibitor of Ornithine Decarboxylase with Antitumor Activity

Dong Joon Kim, Eunmii Roh, Mee-Young Lee, Naomin Oi, Do Young Lim, Myoung Ok Kim, Yong-Heon Cho, Angelo Pugliese, Jung-Hyun Lim, Hanyong Chen, Jun Jin Cho, Jong-Eun Kim, Sun Chul Kang, Souren Paul, Edouard C. Nice, Zong-Guang Zhou, and Canhua Huang

Précis: The characterization of a cytoskeletal protein in metastatic colorectal cancer reveals a new level of regulation required to suppress EMT and invasive phenotypes in cancer cells, and highlights a potential prognostic indicator of survival in colorectal cancer patients.

G0S2 Suppresses Oncogenic Transformation by Regulating a MYC-Related Transcriptional Repressor

Christina Y. Yim, David J. Sekula, Mary P. Hever-Jardine, Sarah J. Freemantle, Ethan Dmitrovsky, and Joshua M. Warzecha

Précis: Mechanistic insights into dry-mouth syndrome widely experienced by head and neck cancer patients receiving radiotherapy suggest that IL6 pretreatment may preserve salivary gland function, relieving this side-effect.

Activating Mutations in PIK3CB Confer Resistance to PI3K Inhibition and Define a Novel Oncogenic Role for p110β

Yoshito Nakamichi, Kimberly Walter, Jill M. Sporer, Carol O’Brien, Ling Y. Huw, Garret M. Hampton, and Mark R. Lackner

Précis: These results define novel mechanisms of resistance to selective PI3K inhibitors in PTEN-deficient breast cancers, with implications for the clinical management of patients undergoing PI3K-targeted treatment.

G0S2 Suppresses Oncogenic Transformation by Repressing a MYC-Regulated Transcriptional Repression Program

Christina Y. Yim, David J. Sekula, Mary P. Hever-Jardine, Xi Liu, Joshua M. Warzecha, Janice Tam, Sarah J. Freemantle, Ethan Dmitrovsky, and Michael I. Spinella

Précis: These findings reveal that a gene implicated in inhibition of lipid breakdown in adipose tissue is required to suppress oncogenesis, perhaps underpinning the malignant behavior of cancer cells where this gene is silenced.

Therapeutics, Targets, and Chemical Biology
An Integrated Analysis of Heterogeneous Drug Responses in Acute Myeloid Leukemia That Enables the Discovery of Predictive Biomarkers

Precis: This study presents a comprehensive new approach to evaluate the efficacy of new anticancer drugs in preclinical models, especially against cancer stem-like cells, helping address a need to identify drug response biomarkers that can improve patient selection criteria for clinical trials.

Dual Targeting of CDK4 and ARK5 Using a Novel Kinase Inhibitor ON123300 Exerts Potent Anticancer Activity against Multiple Myeloma

Precis: These findings offer a preclinical rationale to investigate the clinical application of ARK5 kinase inhibitors in patients with multiple myeloma, to improve therapeutic outcomes.

Activated Thyroid Hormone Promotes Differentiation and Chemotherapeutic Sensitization of Colorectal Cancer Stem Cells by Regulating Wnt and BMP4 Signaling
Veronica Catalano, Monica Dentice, Raffaele Ambrosio, Cristina Luongo, Rosachiarra Carollo, Antonina Benfante, Matteo Todaro, Giorgio Stassi, and Domenico Salvatore

Precis: Thyroid hormone signaling controls the fate of colorectal cancer stem-like cells, including their response to chemotherapy, with immediate clinical implications for a new approach to sensitize stem-like populations in colorectal cancer treatment.

Cancer Stem-like Cells Act via Distinct Signaling Pathways in Promoting Late Stages of Malignant Progression
Victoria da Silva-Diz, Pilar Simón-Extremera, Adrià Bernat-Pegaera, Jana de Sostoa, María Urbí, Rosa M. Penín, Diana Pérez Sidelnikova, Oriol Bermejo, Joan María Viñals, Annie Rodolosse, Eva González-Suárez, Antonio Gómez Moruno, Miguel Ángel Pujana, Manel Esteller, Alberto Villanueva, Francesc Viñals, and Purificación Muñoz

Precis: These findings show how different approaches to target tumor-initiating stem-like cell populations can have divergent effects on the extent of disease recurrence and progression, illustrating a need of greater information in choosing the approach.

Arginine Methylation of SREBP1a via PRMT5 Promotes De Novo Lipogenesis and Tumor Growth
Liu Liu, Xiaoping Zhao, Li Zhao, Jiajin Li, Hao Yang, Zongqing Zhu, Jianjun Liu, and Gang Huang

Precis: This study provides a mechanistic rationale for targeting lipid metabolism that reinforces this therapeutic approach as a generalized strategy to attack cancer cells.

GALNT1-Mediated Glycosylation and Activation of Sonic Hedgehog Signaling Maintains the Self-Renewal and Tumor-Initiating Capacity of Bladder Cancer Stem Cells
Chong Li, Ying Du, Zhao Yang, Luyun He, Yanying Wang, Lu Hao, Mingxia Ding, Ruping Yan, Jiansong Wang, and Zosen Fan

Precis: The identification of a subpopulation of cancer stem-like cells in human bladder tumors that rely on Sonic Hedgehog signaling may provide a point for therapeutic intervention to reduce or prevent relapses in patients.

EGFR Signaling Enhances Aerobic Glycolysis in Triple-Negative Breast Cancer Cells to Promote Tumor Growth and Immune Escape
Seung-Oe Lim, Chia-Wei Li, Weiya Xia, Heng-Huan Lee, Shih-Shin Chang, Ju Shen, Jennifer L. Hsu, Daniel Rafery, Danijel Djukovic, Haiwei Gu, Wei-Chao Chang, Hung-Ling Wang, Mong-Liang Chen, Longfei Huo, Chung-Hsuan Chen, Yun Wu, Aysegul Sahin, Samir M. Hanash, Gabriel N. Hortobagyi, and Mien-Chie Hung

Precis: This study offers a preclinical rationale to combine EGF pathway blockade with glycolytic inhibitors as a strategy to treat triple-negative breast cancer, with immediate implications for clinical investigation.

Correction: Multiplex H. pylori Serology and Risk of Gastric Cardia and Noncardia Adenocarcinomas

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ABOUT THE COVER

Senescence drives loss of salivary gland function following radiation. This image shows immunostaining for decoy receptor 2 (DcR2; brown), a p53 target gene and a marker for cellular senescence, in irradiated mouse salivary glands. Senescent cells in the ductal compartment were found in irradiated mice and also in human patients following radiotherapy. Senescence accompanies loss of function in irradiated salivary glands and is markedly IL6 dependent. Paradoxically, loss of function can also be prevented by IL6 pretreatment, suggesting a possible therapeutic approach to relieve the side-effect of dry-mouth syndrome in irradiated head and neck cancer patients. For details, see article by Marmary and colleagues on page 1170.