

## BREAKING ADVANCES

- 987 Highlights from Recent Cancer Literature


CANCER RESEARCH 75<sup>th</sup> 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  
Shohei Koyama, Esra A. Akbay, Yvonne Y. Li, Amir R. Aref, Ferdinandos Skoulidis, Grit S. Herter-Sprie, Kevin A. Buczkowski, Yan Liu, Mark M. Awad, Warren L. Denning, Lixia Diao, Jing Wang, Edwin R. Parra-Cuentas, Ignacio I. Wistuba, Margaret Soucheray, Tran Thai, Hajime Asahina, Shunsuke Kitajima, Abigail Altabef, Jillian D. Cavanaugh, Kevin Rhee, Peng Gao, Haikuo Zhang, Peter E. Fecci, Takeshi Shimamura, Matthew D. Hellmann, John V. Heymach, F. Stephen Hodi, Gordon J. Freeman, David A. Barbie, Glenn Dranoff, Peter S. Hammerman, and Kwok-Kin Wong
- 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 testing 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, Jaeho 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 IFN $\gamma$  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.

# Table of Contents

## 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, Taehee Kang, Nam Hoon Kwon, Hyo Eun Moon, Sun Ha Paek, Daehee 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

Robyn L. Prueitt, Tiffany A. Wallace, Sharon A. Glynn, Ming Yi, Wei Tang, Jun Luo, Tiffany H. Dorsey, Katherine E. Stagliano, John W. Gillespie, Robert S. Hudson, Atsushi Terunuma, Jennifer L. Shoe, Diana C. Haines, Harris G. Yfantis, Misop Han, Damali N. Martin, Symone V. Jordan, James F. Borin, Michael J. Naslund, Richard B. Alexander, Robert M. Stephens, Christopher A. Loffredo, Dong H. Lee, Nagireddy Putluri, Arun Sreekumar, Arthur A. Hurwitz, and Stefan Ambis

*Précis:* These findings suggest that tissue inflammation and nicotine-induced molecular alterations can accelerate the development of prostate cancer metastasis 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, Zhihui Chen, Annette L. Medhurst, Jessica A. Neal, Zhengqiang Bao, Oliver Mortusewicz, Joanna McGouran, Xinming Song, Huahao 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

Jesus Delgado-Calle, Judith Anderson, Meloney D. Gregor, Masahiro Hiasa, John M. Chirgwin, Nadia Carlesso, Toshiyuki Yoneda, Khalid S. Mohammad, Lilian I. Plotkin, G. David Roodman, and Teresita Bellido

*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- $\kappa$ B and Promotes Aggressiveness in Breast Cancer

Lili Jiang, Liang Yu, Xin Zhang, Fangyong Lei, Lan Wang, Xiangxia Liu, Shu Wu, Jinrong Zhu, Geyan Wu, Lixue Cao, Aibin Liu, Libing Song, and Jun Li

*Précis:* Aberrant microRNA silencing underlies constitutively activated NF- $\kappa$ B 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, Adebayo 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.



# Table of Contents

**1122** PDLIM1 Stabilizes the E-Cadherin/ $\beta$ -Catenin Complex to Prevent Epithelial–Mesenchymal Transition and Metastatic Potential of Colorectal Cancer Cells

Hai-Ning Chen, Kefei Yuan, Na Xie, Kui Wang, Zhao Huang, Yan Chen, Qianhui Dou, Min Wu, 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.

**1135** Cdx2 Expression and Intestinal Metaplasia Induced by *H. pylori* Infection of Gastric Cells Is Regulated by NOD1-Mediated Innate Immune Responses

Naoki Asano, Akira Imatani, Tomohiro Watanabe, Jun Fushiya, Yutaka Kondo, Xiaoyi Jin, Nobuyuki Ara, Kaname Uno, Katsunori Iijima, Tomoyuki Koike, Warren Strober, and Tooru Shimosegawa

*Précis:* A molecule that recognizes bacterial patterns in cells controls the attitude of the innate immune system to a bacterial infection of the stomach that is common in much of the world, thereby influencing risks initiation and progression of stomach cancers.

## PREVENTION AND EPIDEMIOLOGY

**1146** Herbacetin Is a Novel Allosteric Inhibitor of Ornithine Decarboxylase with Antitumor Activity

Dong Joon Kim, Eunmiri Roh, Mee-Hyun Lee, Naomi Oi, Do Young Lim, Myoung Ok Kim, Yong-Yeon Cho, Angelo Pugliese, Jung-Hyun Shim, Hanyong Chen, Eun Jin Cho, Jong-Eun Kim, Sun Chul Kang, Souren Paul, Hee Eun Kang, Ji Won Jung, Sung-Young Lee, Sung-Hyun Kim, Kanamata Reddy, Young Il Yeom, Ann M. Bode, and Zigang Dong

*Précis:* Human tumors are addicted to polyamine synthesis, the inhibition of which, by a new natural product identified in this study, can exert antitumor and chemopreventive activity in preclinical models of colon cancer without significant cytotoxic effects.

## THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

**1158** The CDK9 Inhibitor Dinaciclib Exerts Potent Apoptotic and Antitumor Effects in Preclinical Models of MLL-Rearranged Acute Myeloid Leukemia

Adele Baker, Gareth P. Gregory, Inge Verbrugge, Lev Kats, Joshua J. Hilton, Eva Vidacs, Erwin M. Lee, Richard B. Lock, Johannes Zuber, Jake Shortt, and Ricky W. Johnstone

*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.

**1170** Radiation-Induced Loss of Salivary Gland Function Is Driven by Cellular Senescence and Prevented by IL6 Modulation

Yitzhak Marmary, Revital Adar, Svetlana Gaska, Annette Wygoda, Alexander Maly, Jonathan Cohen, Ron Eliashar, Lina Mizrahi, Carmit Orfaig-Geva, Bruce J. Baum, Stefan Rose-John, Eithan Galun, and Jonathan H. Axelrod

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

**1181** Peptide–Drug Conjugate GnRH–Sunitinib Targets Angiogenesis Selectively at the Site of Action to Inhibit Tumor Growth

Orestis Argyros, Theodoros Karamelas, Xenophon Asvos, Aimilia Varela, Nisar Sayyad, Athanasios Papakyriakou, Constantinos H. Davos, Andreas G. Tzakos, Demosthenes Fokas, and Constantin Tamvakopoulos

*Précis:* These findings suggest that the systemic toxic effects of antiangiogenic therapy with the tyrosine kinase inhibitor sunitinib can be greatly minimized by a general hormone-based targeting strategy, with immediate clinical implications for evaluation in combination studies for many cancers.

**1193** Activating Mutations in *PIK3CB* Confer Resistance to PI3K Inhibition and Define a Novel Oncogenic Role for p110 $\beta$



Yoshito Nakanishi, Kimberly Walter, Jill M. Spoerke, 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.

**1204** G0S2 Suppresses Oncogenic Transformation by Repressing a MYC-Regulated Transcriptional 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 J. 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.

# Table of Contents

- 1214** **An Integrated Analysis of Heterogeneous Drug Responses in Acute Myeloid Leukemia That Enables the Discovery of Predictive Biomarkers**  
Weihsu C. Chen, Julie S. Yuan, Yan Xing, Amanda Mitchell, Nathan Mbong, Andreea C. Popescu, Jessica McLeod, Gitte Gerhard, James A. Kennedy, Goce Bogdanoski, Stevan Lauriault, Sofie Perdu, Yulia Merkulova, Mark D. Minden, Donna E. Hogge, Cynthia Guidos, John E. Dick, and Jean C.Y. Wang  
*Précis:* 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.
- 1225** **Dual Targeting of CDK4 and ARK5 Using a Novel Kinase Inhibitor ON123300 Exerts Potent Anticancer Activity against Multiple Myeloma**  
Deepak Perumal, Pei-Yu Kuo, Violetta V. Leshchenko, Zewei Jiang, Sai Krishna Athaluri Divakar, Hearn Jay Cho, Ajai Chari, Joshua Brody, M.V. Ramana Reddy, Weijia Zhang, E. Premkumar Reddy, Sundar Jagannath, and Samir Parekh  
*Précis:* These findings offer a preclinical rationale to investigate the clinical application of ARK5 kinase inhibitors in patients with multiple myeloma, to improve therapeutic outcomes.
- TUMOR AND STEM CELL BIOLOGY**
- 1237** **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, Rosachiara Carollo, Antonina Benfante, Matilde Todaro, Giorgio Stassi, and Domenico Salvatore  
*Précis:* 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.
- 1245** **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-Peguera, Jana de Sostoa, Maria Urpí, Rosa M. Penín, Diana Pérez Sidelnikova, Oriol Bermejo, Joan Maria Viñals, Annie Rodolosse, Eva González-Suárez, Antonio Gómez Moruno, Miguel Ángel Pujana, Manel Esteller, Alberto Villanueva, Francesc Viñals, and Purificación Muñoz  
*Précis:* 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.
- 1260** **Arginine Methylation of SREBP1a via PRMT5 Promotes *De Novo* Lipogenesis and Tumor Growth**  
Liu Liu, Xiaoping Zhao, Li Zhao, Jiajin Li, Hao Yang, Zongping Zhu, Jianjun Liu, and Gang Huang  
*Précis:* This study provides a mechanistic rationale for targeting lipid metabolism that reinforces this therapeutic approach as a generalized strategy to attack cancer cells.
- 1273** **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 Zusen Fan  
*Précis:* 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.
- 1284** **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, Jia Shen, Jennifer L. Hsu, Daniel Raftery, 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  
*Précis:* 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

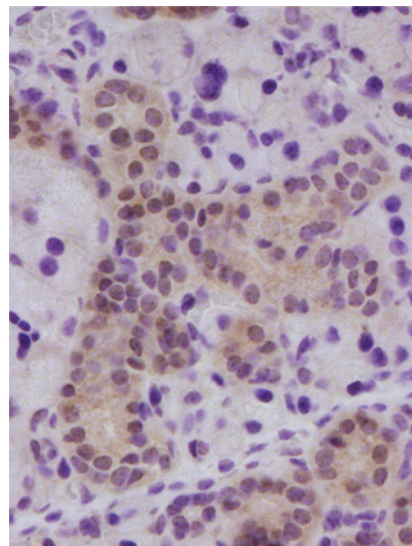
- 1297** **Correction: Multiplex *H. pylori* Serology and Risk of Gastric Cardia and Noncardia Adenocarcinomas**

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# Table of Contents

## 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.



# Cancer Research

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