

BREAKING ADVANCES

- 10017 | **Highlights from Recent Cancer Literature**

REVIEWS

- 10019 | **Imaging Cycling Tumor Hypoxia**
Shingo Matsumoto, Hironobu Yasui, James B. Mitchell, and Murali C. Krishna
- 10024 | **Targeting $\gamma\delta$ T Lymphocytes for Cancer Immunotherapy: From Novel Mechanistic Insight to Clinical Application**
Anita Q. Gomes, Duarte S. Martins, and Bruno Silva-Santos

PERSPECTIVES

- 10028 | **XMRV: A New Virus in Prostate Cancer?**
Amanda L. Aloia, Karen S. Sfanos, William B. Isaacs, Qizhi Zheng, Frank Maldarelli, Angelo M. De Marzo, and Alan Rein

MEETING REPORT

- 10034 | **Twenty-Second Annual Pezcoller Symposium: RNA Biology and Cancer**
René Bernards, Witold Filipowicz, David M. Livingston, and Enrico Mihich

PRIORITY REPORTS

- 10038 | **The Neuroblastoma-Associated F1174L ALK Mutation Causes Resistance to an ALK Kinase Inhibitor in ALK-Translocated Cancers**
Takaaki Sasaki, Katsuhiko Okuda, Wei Zheng, James Butrynski, Marzia Capelletti, Liping Wang, Nathanael S. Gray, Keith Wilner, James G. Christensen, George Demetri, Geoffrey I. Shapiro, Scott J. Rodig, Michael J. Eck, and Pasi A. Jänne
- Précis:* Identifying acquired mutations that confer resistance to targeted inhibitors represents a first step in developing second-generation drugs and strategies to preserve the efficacy of the original targeting strategy.

- 10044 | **Human Bone Marrow-Derived MSCs Can Home to Orthotopic Breast Cancer Tumors and Promote Bone Metastasis**
Robert H. Goldstein, Michaela R. Reagan, Kristen Anderson, David L. Kaplan, and Michael Rosenblatt

Précis: Mesenchymal stem cells home to primary breast cancer tumors from physiologic bone environments, promoting tumor growth and skeletal and visceral metastases.

INTEGRATED SYSTEMS AND TECHNOLOGIES

- 10051 | **Mathematical and Experimental Approaches to Identify and Predict the Effects of Chemotherapy on Neuroglial Precursors**
Olivier Hyrien, Jörg Dietrich, and Mark Noble

Précis: Chemotherapeutic drugs may alter precursor cell function in multiple ways, including cell cycle length, the time between division and differentiation, and the probability of self-renewal division, with potential clinical implications.

- 10060 | **Coexpression Network Analysis Identifies Transcriptional Modules Related to Proastrocytic Differentiation and Sprouty Signaling in Glioma**
Alexander E. Ivliev, Peter A.C. 't Hoen, and Marina G. Sergeeva

Précis: Study identifies a proastrocytic gene expression signature with prognostic utility in brain tumors and reveals that Sprouty family proteins which modify EGF signaling likely participate in brain cancer pathogenesis.

- 10071 | **Integrated Optical Coherence Tomography and Microscopy for Ex Vivo Multiscale Evaluation of Human Breast Tissues**
Chao Zhou, David W. Cohen, Yihong Wang, Hsiang-Chieh Lee, Amy E. Mondelblatt, Tsung-Han Tsai, Aaron D. Aguirre, James G. Fujimoto, and James L. Connolly

Précis: Findings lay the foundation to improve optical evaluation of breast tissues with 3D imaging technologies that could improve surgical management of cancer.

10080 **Expression of Snail in Epidermal Keratinocytes Promotes Cutaneous Inflammation and Hyperplasia Conducive to Tumor Formation**
Fei Du, Yoshikazu Nakamura, Tuan-Lin Tan, Pedro Lee, Robert Lee, Benjamin Yu, and Colin Jamora

Précis: Findings suggest that the chief contribution of a key EMT-inducing transcription factor to carcinoma progression is largely through the creation of a hyperproliferative and inflammatory niche in the tumor microenvironment.

10090 **HGF/c-Met Acts as an Alternative Angiogenic Pathway in Sunitinib-Resistant Tumors**
Farbod Shojaei, Joseph H. Lee, Brett H. Simmons, Anthony Wong, Carlos O. Esparza, Pamela A. Plumlee, Junli Feng, Albert E. Stewart, Dana D. Hu-Lowe, and James G. Christensen

Précis: Results indicate that inhibition of the c-Met pathway has an additive effect on inhibition of the VEGF pathway in tumors resistant to the VEGF inhibitor sunitinib.

10101 **HIF-2 α Enhances β -Catenin/TCF-Driven Transcription by Interacting with β -Catenin**
Hyunsung Choi, Yang-Sook Chun, Tae-You Kim, and Jong-Wan Park

Précis: Findings suggest that HIF-1 α /HIF-2 α balance determines cell growth when hypoxia and Wnt stimulation coexist, affecting understanding of tumor fate under hypoxic conditions that may help control hypoxic tumor cells.

10112 **IL-17 Enhances Tumor Development in Carcinogen-Induced Skin Cancer**
Lin Wang, Tangsheng Yi, Wang Zhang, Drew M. Pardoll, and Hua Yu

Précis: Activation of a central proinflammatory pathway for adaptive immune cells contributes to cancer-associated inflammation in a classical model of carcinogenesis.

10121 **Delivery of NKG2D Ligand Using an Anti-HER2 Antibody-NKG2D Ligand Fusion Protein Results in an Enhanced Innate and Adaptive Antitumor Response**
Hyun-Mi Cho, Joseph D. Rosenblatt, Khaled Tolba, Sarah J. Shin, Daniel S. Shin, Carmen Calfa, Yu Zhang, and Seung-Uon Shin

Précis: Preclinical study defines a novel antibody-based therapeutic strategy that can couple innate and adaptive immune responses against tumors to increase antitumor efficacy.

10131 **Conditional Deletion of the Focal Adhesion Kinase FAK Alters Remodeling of the Blood-Brain Barrier in Glioma**
Jisook Lee, Alexandra K. Borboa, Hyun Bae Chun, Andrew Baird, and Brian P. Eliceiri

Précis: Findings suggest a way to stabilize the tumor vasculature as a strategy to treat brain tumors, including how blood-brain barriers might be restored in this setting.

10141 **Longitudinal, Noninvasive Imaging of T-Cell Effector Function and Proliferation in Living Subjects**
Manishkumar R. Patel, Ya-Fang Chang, Ian Y. Chen, Michael H. Bachmann, Xinrui Yan, Christopher H. Contag, and Sanjiv S. Gambhir

Précis: This is the first study of its kind to noninvasively visualize T-cell receptor-dependent T-cell activation and differentiation in small animals in response to tumor antigens.

10150 **Active Immunotherapy Induces Antibody Responses That Target Tumor Angiogenesis**
Jonathan Schoenfeld, Masahisa Jinushi, Yukoh Nakazaki, Daniel Wiener, Joosang Park, Robert Soiffer, Donna Neuberg, Martin Mihm, F. Stephen Hodi, and Glenn Dranoff

Précis: Cancer vaccines may stimulate in patients a humoral reaction that broadly targets tumor angiogenesis.

10161 **The Inflammasome Component Nlrp3 Impairs Antitumor Vaccine by Enhancing the Accumulation of Tumor-Associated Myeloid-Derived Suppressor Cells**
Hendrik W. van Deventer, Joseph E. Burgents, Qing Ping Wu, Rita-Marie T. Woodford, W. June Brickey, Irving C. Allen, Erin McElvania-Tekippe, Jonathan S. Serody, and Jenny P.-Y. Ting

Précis: Results identify a core component of the inflammasome as an unexpected mediator of tumoral immune escape by myeloid-derived suppressor cells, also implicating it as a target to improve responses to dendritic cell vaccines of major interest in cancer immunotherapy.

10170 **CXCL12 Mediates Immunosuppression in the Lymphoma Microenvironment after Allogeneic Transplantation of Hematopoietic Cells**
Christoph Dürr, Dietmar Pfeifer, Rainer Claus, Annette Schmitt-Graeff, Ulrike V. Gerlach, Ralph Graeser, Sophie Krüger, Armin Gerbitz, Robert S. Negrin, Jürgen Finke, and Robert Zeiser

Précis: Findings suggest a mechanistic strategy to degrade immune suppression and improve efficacy in cancer patients who receive bone marrow transplant therapy.

10182 **Prognostic Value and Function of KLF4 in Prostate Cancer: RNAi and Vector-Mediated Overexpression Identify KLF4 as an Inhibitor of Tumor Cell Growth and Migration**

Ji Wang, Robert F. Place, Vera Huang, Xiaoling Wang, Emily J. Noonan, Clara E. Magyar, Jiaoti Huang, and Long-Cheng Li

Précis: A potential tumor and metastasis suppressor gene is identified in prostate cancer, in which its decreased expression predicts the development of metastasis.

10192 **Free Tubulin Modulates Mitochondrial Membrane Potential in Cancer Cells**

Eduardo N. Maldonado, Jyoti Patnaik, Matthew R. Mullins, and John J. Lemasters

Précis: Results suggest a mechanism to understand how mitochondrial metabolism is suppressed in cancer cells, a characteristic feature of the Warburg effect.

10202 **A Unique Metastasis Gene Signature Enables Prediction of Tumor Relapse in Early-Stage Hepatocellular Carcinoma Patients**

Stephanie Roessler, Hu-Liang Jia, Anuradha Budhu, Marshonna Forgues, Qing-Hai Ye, Ju-Seog Lee, Snorri S. Thorgeirsson, Zhongtang Sun, Zhao-You Tang, Lun-Xiu Qin, and Xin Wei Wang

Précis: Results from two independent cohorts with mixed etiologies and ethnicity define a unique metastasis expression signature that can predict early recurrence of hepatocellular carcinoma.

10213 **Downregulation of c-MYC Protein Levels Contributes to Cancer Cell Survival under Dual Deficiency of Oxygen and Glucose**

Hiroaki Okuyama, Hiroko Endo, Tamaki Akashika, Kikuya Kato, and Masahiro Inoue

Précis: c-MYC downregulation may represent a universal survival strategy of cancer cells under ischemic conditions that select for development of aggressive phenotypes.

Tip30 Deletion in MMTV-Neu Mice Leads to Enhanced EGFR Signaling and Development of Estrogen Receptor-Positive and Progesterone Receptor-Negative Mammary Tumors

Chengliang Zhang, Mikito Mori, Shenglan Gao, Aimin Li, Isamu Hoshino, Mark D. Aupperlee, Sandra Z. Haslam, and Hua Xiao

Précis: Mechanistic study leads to development of a mouse model of ER⁺/PR⁻ breast cancer, which while not as widely studied as other disease subtypes accounts for up to 25% of all breast cancers.

Histone H3 Lysine 79 Methyltransferase Dot1 Is Required for Immortalization by MLL Oncogenes

Ming-Jin Chang, Hongyu Wu, Nicholas J. Achille, Mary Rose Reisenauer, Chau-Wen Chou, Nancy J. Zeleznik-Le, Charles S. Hemenway, and Wenzheng Zhang

Précis: Findings define a pivotal requirement for an important histone methyltransferase in a class of clinically aggressive leukemias, also implicating this enzyme as a therapeutic target for novel treatment strategies in these diseases.

THERAPEUTICS, TARGETS,
AND CHEMICAL BIOLOGY

Dual Functional Monoclonal Antibody PF-04605412 Targets Integrin $\alpha 5 \beta 1$ and Elicits Potent Antibody-Dependent Cellular Cytotoxicity

Gang Li, Lianglin Zhang, Enhong Chen, Jianying Wang, Xin Jiang, Jeffrey H. Chen, Grant Wickman, Karin Amundson, Simon Bergqvist, James Zobel, Dana Buckman, Sangita M. Baxi, Steven L. Bender, Gerald F. Casperson, and Dana D. Hu-Lowe

Précis: Findings suggest that the efficacy of antibody-based therapy of solid tumors can be improved by engineering changes in the antibody constant region that enhance ADCC.

- 10255 **Targeting the Mitotic Checkpoint for Cancer Therapy with NMS-P715, an Inhibitor of MPS1 Kinase**
Riccardo Colombo, Marina Caldarelli, Milena Mennecozzi, Maria Laura Giorgini, Francesco Sola, Paolo Cappella, Claudia Perrera, Stefania Re Depaolini, Luisa Rusconi, Ulisse Cucchi, Nilla Avanzi, Jay Aaron Bertrand, Roberto Tiberio Bossi, Enrico Pesenti, Arturo Galvani, Antonella Isacchi, Francesco Colotta, Daniele Donati, and Jürgen Moll
- Précis:* Proof-of-concept findings based on a small molecule that targets a key mitotic checkpoint suggest a promising new approach to selectively destroy cancer cells.
- 10265 **Loss of Metallothionein Predisposes Mice to Diethylnitrosamine-Induced Hepatocarcinogenesis by Activating NF- κ B Target Genes**
Sarmila Majumder, Satavisha Roy, Thomas Kaffenberger, Bo Wang, Stefan Costinean, Wendy Frankel, Anna Bratasz, Periannan Kuppusamy, Tsonwin Hai, Kalpana Ghoshal, and Samson T. Jacob
- Précis:* Results demonstrate the important protective role of metallothioneins as free radical scavengers during chemical carcinogen-induced liver cancer.
- 10277 **Transcriptional Control of the ERBB2 Amplicon by ERR α and PGC-1 β Promotes Mammary Gland Tumorigenesis**
Geneviève Deblois, Ghada Chahrour, Marie-Claude Perry, Guillaume Sylvain-Drolet, William J Muller, and Vincent Giguère
- Précis:* This study identifies two transcription factors that influence breast cancer etiology by coordinating the expression of genes located in the 17q12 region surrounding HER2.
- 10288 **CX-4945, an Orally Bioavailable Selective Inhibitor of Protein Kinase CK2, Inhibits Prosurvival and Angiogenic Signaling and Exhibits Antitumor Efficacy**
Adam Siddiqui-Jain, Denis Drygin, Nicole Streiner, Peter Chua, Fabrice Pierre, Sean E. O'Brien, Josh Bliesath, Mayuko Omori, Nanni Huser, Caroline Ho, Chris Proffitt, Michael K. Schwabe, David M. Ryckman, William G. Rice, and Kenna Anderes
- Précis:* Study offers preclinical validation of a first-in-class orally bioavailable inhibitor of the nononcogenic protein kinase CK2.
- 10299 **Pemetrexed Indirectly Activates the Metabolic Kinase AMPK in Human Carcinomas**
Scott B. Rothbart, Alexandra C. Racanelli, and Richard G. Moran
- Précis:* A folate antimetabolite currently approved by the FDA is found to also target the AMPK and mTORC metabolic pathways, broadening the range of its potential clinical applications.
- 10310 **NEDD8-Targeting Drug MLN4924 Elicits DNA Rereplication by Stabilizing Cdt1 in S Phase, Triggering Checkpoint Activation, Apoptosis, and Senescence in Cancer Cells**
Jie Jessie Lin, Michael A. Milhollen, Peter G. Smith, Usha Narayanan, and Anindya Dutta
- Précis:* Findings reveal insights into the mechanism of action of an important new drug in clinical trials, also showing that even its transient exposure to p53 mutant cancer cells may be sufficient to produce potent anticancer effects.
- 10321 **ASNA-1 Activity Modulates Sensitivity to Cisplatin**
Oskar Hemmingsson, Gautam Kao, Maria Still, and Peter Naredi
- Précis:* C. elegans offers a model to characterize cancer drug resistance mechanisms in different genetic backgrounds, used here to define a targetable mechanism of cisplatin resistance.
- 10329 **Zoledronic Acid Potentiates mTOR Inhibition and Abolishes the Resistance of Osteosarcoma Cells to RAD001 (Everolimus): Pivotal Role of the Prenylation Process**
Gatien Moriceau, Benjamin Ory, Laura Mitrofan, Chiara Riganti, Frédéric Blanchard, Régis Brion, Céline Charrier, Séverine Battaglia, Paul Pilet, Marc G. Denis, Leonard D. Shultz, Jukka Mönkkönen, Françoise Rédini, and Dominique Heymann
- Précis:* Combining inhibitors of the mTOR pathway with protein prenylation pathways such as zoledronate might markedly improve treatment of osteosarcoma, a highly aggressive disease.

10340

Regulation of the Embryonic Morphogen Nodal by Notch4 Facilitates Manifestation of the Aggressive Melanoma Phenotype

Katharine M. Hardy, Dawn A. Kirschmann, Elisabeth A. Seftor, Naira V. Margaryan, Lynne-Marie Postovit, Luigi Strizzi, and Mary J.C. Hendrix

Précis: Findings define elements of a critical signaling pathway in development of metastatic melanoma that may be therapeutically tractable to disruption by Notch4 receptor antibodies.

10351

Combinatorial Regulation of Neuroblastoma Tumor Progression by N-Myc and Hypoxia Inducible Factor HIF-1 α

Guoliang Qing, Nicolas Skuli, Patrick A. Mayes, Bruce Pawel, Daniel Martinez, John M. Maris, and M. Celeste Simon

Précis: Lactate dehydrogenase is defined as a metabolic weakness of N-Myc-amplified neuroblastoma, providing an attractive therapeutic target in this aggressive and poorly managed pediatric cancer.

10362

Mage-A Cancer/Testis Antigens Inhibit p53 Function by Blocking Its Interaction with Chromatin

Lynnette Marcar, Nicola J. MacLaine, Ted R. Hupp, and David W. Meek

Précis: Findings define a mechanism through which cells may gain metastatic capability by defeating p53 function, with implications for cancer immunotherapies that target MAGE antigens.

10371

Homeoprotein Six1 Increases TGF- β Type I Receptor and Converts TGF- β Signaling from Suppressive to Supportive for Tumor Growth

Douglas S. Micalizzi, Chu-An Wang, Susan M. Farabaugh, William P. Schiemann, and Heide L. Ford

Précis: A transcription factor that promotes epithelial-mesenchymal transition in breast cancer is shown to support metastatic properties by upregulating the type I receptor for TGF β .

10381

p38 Kinase Is Crucial for Osteopontin-Induced Furin Expression That Supports Cervical Cancer Progression

Vinit Kumar, Reeti Behera, Kirti Lohite, Swapnil Karnik, and Gopal C Kundu

Précis: Mechanistic studies of the regulation of osteopontin, an important proinvasive cytokine in the tumor microenvironment, suggest novel approaches to combat cervical cancer.

Paxillin Predicts Survival and Relapse in Non-Small Cell Lung Cancer by MicroRNA-218 Targeting

De-Wei Wu, Ya-Wen Cheng, John Wang, Chih-Yi Chen, and Huei Lee

Précis: Findings reveal how frequent misregulation of a miRNA-controlled cell adhesion pathway can contribute to poor clinical outcomes in lung cancer, with implications for new therapeutic targeting strategies.

10402

Role of Survivin in EGFR Inhibitor-Induced Apoptosis in Non-Small Cell Lung Cancers Positive for EGFR Mutations

Kunio Okamoto, Isamu Okamoto, Wataru Okamoto, Kaoru Tanaka, Ken Takezawa, Kiyoko Kuwata, Haruka Yamaguchi, Kazuto Nishio, and Kazuhiko Nakagawa

Précis: Mechanistic findings define two critical pathways which are likely to sustain the survival of lung adenocarcinoma cells treated with EGFR kinase inhibitors, with implications for the design of combination drug therapies to be tested in clinic.

10411

CXCR4 Signaling Regulates Metastasis of Chemoresistant Melanoma Cells by a Lymphatic Metastatic Niche

Minah Kim, Young Jun Koh, Kyung Eun Kim, Bong Ihn Koh, Do-Hyun Nam, Kari Alitalo, Injune Kim, and Gou Young Koh

Précis: Lymphatic metastatic niches can support a distinct chemoresistant cell population in melanoma, suggesting new combinational drug strategies to improve melanoma therapy.

10422

p53 Dysfunction by Xeroderma Pigmentosum Group C Defects Enhance Lung Adenocarcinoma Metastasis via Increased Mmp1 Expression

Yi-Hui Wu, Tzu-Chin Wu, Jiunn-Wang Liao, Kun-Tu Yeh, Chih-Yi Chen, and Huei Lee

Précis: Findings define a mechanism of p53 dysfunction that can promote metastasis by directly altering expression of an extracellular matrix metalloprotease.

10433 | **Coexpression of Oct4 and Nanog Enhances Malignancy in Lung Adenocarcinoma by Inducing Cancer Stem Cell-Like Properties and Epithelial-Mesenchymal Transdifferentiation**
Shih-Hwa Chiou, Mong-Lien Wang, Yu-Ting Chou, Chi-Jen Chen, Chun-Fu Hong, Wang-Ju Hsieh, Hsin-Tzu Chang, Ying-Shan Chen, Tzu-Wei Lin, Han-Sui Hsu, and Cheng-Wen Wu

Précis: Findings establish roles for two central embryonic stemness factors in promoting lung cancer metastasis.

10445 | **Cell Cycle Regulator ING4 Is a Suppressor of Melanoma Angiogenesis That Is Regulated by the Metastasis Suppressor BRMS1**
Jun Li and Gang Li

Précis: Findings suggest that restoring the function of the ING4 tumor suppressor gene could not only block cell proliferation but also angiogenesis and metastasis of human melanoma.

10454 | **Pierce1, a Novel p53 Target Gene Contributing to the Ultraviolet-Induced DNA Damage Response**

Young Hoon Sung, Hye Jin Kim, Sushil Devkota, Jusik Roh, Jaehoon Lee, Kunsoo Rhee, Young Yil Bahk, and Han-Woong Lee

Précis: A novel p53 target gene contributes to proper induction of the DNA damage response in UVC-irradiated cells.

10464 | **The Canonical NF- κ B Pathway Governs Mammary Tumorigenesis in Transgenic Mice and Tumor Stem Cell Expansion**
Manran Liu, Toshiyuki Sakamaki, Mathew C. Casimiro, Nicole E. Willmarth, Andrew A. Quong, Xiaoming Ju, John Ojeifo, Xuanmao Jiao, Wen-Shuz Yeow, Sanjay Katiyar, L. Andrew Shirley, David Joyce, Michael P. Lisanti, Christopher Albanese, and Richard G. Pestell

Précis: This report generates for the first time tissue-specific inducible transgenic mice which establish the role of endogenous NF- κ B in mammary tumor onset and progression in an immune-competent animal.

10474 | **Identification of PP2A Complexes and Pathways Involved in Cell Transformation**
Anna A. Sablina, Melissa Hector, Nathalie Colpaert, and William C. Hahn

Précis: Findings elucidate key effector elements of the signaling pathway through which the SV40 small T antigen supports neoplastic transformation of normal human cells.

RETRACTION

10485 | **Retraction: Tripeptidyl-Peptidase II Controls DNA Damage Responses and In Vivo γ -Irradiation Resistance of Tumors**
Rickard Glas, Alf Grandien, Steven Applequist, Brita Kunert, and Rajender Naredla

10486 | **Acknowledgment to Reviewers**

ABOUT THE COVER

Immunofluorescence analysis of Notch4 (red) and Nodal (green) in C8161 human metastatic melanoma cells reveals the expression of these proteins in a subpopulation of these aggressive cells in culture. An anti-pan-Cadherin antibody (pink) labels the cell membrane. Cell nuclei were counterstained with DAPI (blue). For details, see the article by Hardy and colleagues on page 10340 of this issue.

