

BREAKING ADVANCES

- 6685 | **Highlights from Recent Cancer Literature**

REVIEWS

- 6687 | **Tippling the Balance: Cdk2 Enables Myc to Suppress Senescence**
Per Hydbring and Lars-Gunnar Larsson
- 6692 | **Magnetic Resonance Metabolomics of Intact Tissue: A Biotechnological Tool in Cancer Diagnostics and Treatment Evaluation**
Tone F. Bathen, Beathe Sitter, Torill E. Sjøbakk, May-Britt Tessem, and Ingrid S. Gribbestad

PRIORITY REPORT

- 6697 | **Loss of PTEN Binding Adapter Protein NHERF1 from Plasma Membrane in Glioblastoma Contributes to PTEN Inactivation**
Jennifer R. Molina, Fabiana C. Morales, Yuho Hayashi, Kenneth D. Aldape, and Maria-Magdalena Georgescu
- Précis:* An important new mechanism of inactivation of PTEN tumor suppressor function is revealed in brain tumors.

INTEGRATED SYSTEMS AND TECHNOLOGIES

- 6704 | **Identification of Optimal Drug Combinations Targeting Cellular Networks: Integrating Phospho-Proteomics and Computational Network Analysis**
Sergio Iadevaia, Yiling Lu, Fabiana C. Morales, Gordon B. Mills, and Prahlad T. Ram
- Précis:* Simple and reliable strategies are needed to identify optimal combinations of molecular targeted drugs to treat individual cancer patients, to realize the fullest potential of a targeted therapeutic approach.

- 6715 | **Functional Roles of Multiple Feedback Loops in Extracellular Signal-Regulated Kinase and Wnt Signaling Pathways That Regulate Epithelial-Mesenchymal Transition**
Sung-Young Shin, Oliver Rath, Armin Zebisch, Sang-Mok Choo, Walter Kolch, and Kwang-Hyun Cho

Précis: A systems level analysis reveals a key role for the Raf kinase inhibitor RKIP in modifying feedback loops that determine EMT and invasive cancer cell behavior.

MICROENVIRONMENT AND IMMUNOLOGY

- 6725 | **Tumor-Specific CD8⁺ T Cells Expressing Interleukin-12 Eradicate Established Cancers in Lymphodepleted Hosts**
Sid P. Kerkar, Pawel Muranski, Andrew Kaiser, Andrea Boni, Luis Sanchez-Perez, Zhiya Yu, Douglas C. Palmer, Robert N. Reger, Zachary A. Borman, Ling Zhang, Richard A. Morgan, Luca Gattinoni, Steven A. Rosenberg, Giorgio Trinchieri, and Nicholas P. Restifo

Précis: Methods to engineer a more effective T-cell attack on tumor cells are described that involve overproduction of IL-12 by the T cell in the tumor microenvironment.

MOLECULAR AND CELLULAR PATHOBIOLOGY

- 6735 | **FZD4 as a Mediator of ERG Oncogene-Induced WNT Signaling and Epithelial-to-Mesenchymal Transition in Human Prostate Cancer Cells**
Santosh Gupta, Kristiina Iljin, Henri Sara, John Patrick Mpindi, Tuomas Mirtti, Paula Vainio, Juha Rantala, Kalle Alanen, Matthias Nees, and Olli Kallioniemi

Précis: Findings offer mechanistic insight into how oncogenic ERG activations that occur in many prostate cancers promote EMT and loss of cell adhesion.

6746 **Recruitment of Phosphorylated NPM1 to Sites of DNA Damage through RNF8-Dependent Ubiquitin Conjugates**

Ayaka Koike, Hiroyuki Nishikawa, Wenwen Wu, Yukinori Okada, Ashok R. Venkitaraman, and Tomohiko Ohta

Précis: Findings suggest a novel component of the mechanism by which tumor suppressor BRCA1 mediates DNA double strand break repair and chemosensitivity in human cancers.

6757 **Spi-1/PU.1 Oncogene Accelerates DNA Replication Fork Elongation and Promotes Genetic Instability in the Absence of DNA Breakage**

Pauline Rimmelé, Jun Komatsu, Philippe Hupé, Christophe Roulin, Emmanuel Barillot, Marie Dutreix, Emmanuel Conseiller, Aaron Bensimon, Françoise Moreau-Gachelin, and Christel Guillouf

Précis: Findings suggest hitherto unsuspected functions for an oncogenic basal transcription factor in promoting genomic instability and leukemia development.

6767 **CDX2 Regulates Multidrug Resistance 1 Gene Expression in Malignant Intestinal Epithelium**

Yuji Takakura, Takao Hinoi, Naohide Oue, Tatsunari Sasada, Yasuo Kawaguchi, Masazumi Okajima, Aytekin Akyol, Eric R. Fearon, Wataru Yasui, and Hideki Ohdan

Précis: Study identifies a novel regulator of basal expression of MDR1, a central regulator of drug excretion and absorption in the lower gastrointestinal tract, with implications for understanding drug resistant gastrointestinal tumors.

PREVENTION AND EPIDEMIOLOGY

6779 **Human Chorionic Gonadotropin in Pregnancy and Maternal Risk of Breast Cancer**

Paolo Toniolo, Kjell Grankvist, Marianne Wulff, Tianhui Chen, Robert Johansson, Helena Schock, Per Lenner, Göran Hallmans, Matti Lehtinen, Rudolf Kaaks, Göran Wadell, Anne Zeleniuch-Jacquotte, Eva Lundin, and Annkatrin Lukanova

Précis: Study reveals a mechanistic basis for the long established association between pregnancy and maternal breast cancer risk.

6787 **Combinatorial Chemoprevention Reveals a Novel Smoothened-Independent Role of GLI1 in Esophageal Carcinogenesis**

Sumera Rizvi, Cathrine J. DeMars, Andrea Comba, Vladimir G. Gainullin, Zaheer Rizvi, Luciana L. Almada, Kenneth Wang, Gwen Lomberk, Martin E. Fernández-Zapico, and Navtej S. Buttar

Précis: Study defines a pathway in esophageal carcinogenesis that can be effectively targeted by combinatorial chemoprevention with aspirin and Urso, a compound that decreases injury-inducing bile salts.

6797 **Cell Selection as Driving Force in Lung and Colon Carcinogenesis**

Helmut Schöllnberger, Niko Beerenwinkel, Rudolf Hoogenveen, and Paolo Vineis

Précis: Mathematical modeling of carcinogenesis suggests that mutation rate is less important than Darwinian selection as a driving force in cancer development.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

6804 **PIK3CA Mutation Uncouples Tumor Growth and Cyclin D1 Regulation from MEK/ERK and Mutant KRAS Signaling**

Ensar Halilovic, Qing-Bai She, Qing Ye, Raymond Pagliarini, William R. Sellers, David B. Solit, and Neal Rosen

Précis: Findings suggest that tumors with both KRAS and PI3K mutations are unlikely to respond to inhibition of the MEK pathway alone but will require effective inhibition of both MEK and PI3K/AKT pathway signaling.

6815 **Immunoliposomal Delivery of ²¹³Bi for α -Emitter Targeting of Metastatic Breast Cancer**

Mohanambe Lingappa, Hong Song, Sarah Thompson, Frank Bruchertseifer, Alfred Morgenstern, and George Sgouros

Précis: Liposomes carrying radiolabeled antibodies are effective in delivering alpha particle emitters for metastatic breast cancer therapy.

- 6824 **Inactivation of the Orphan Nuclear Receptor TR3/Nur77 Inhibits Pancreatic Cancer Cell and Tumor Growth**
Syng-Ook Lee, Maen Abdelrahim, Kyungsil Yoon, Sudhakar Chintharlapalli, Sabitha Papineni, Kyoungyun Kim, Huamin Wang, and Stephen Safe
Précis: Findings offer preclinical validation of a tractable, druggable molecule that has been implicated in the control of cancer cell survival at the levels of transcription as well as switching Bcl-2 function at mitochondria.
- 6837 **Aminoflavone, a Ligand of the Aryl Hydrocarbon Receptor, Inhibits HIF-1 α Expression in an AhR-Independent Fashion**
Erika Terzuoli, Maura Puppo, Annamaria Rapisarda, Badarch Uranchimeg, Liang Cao, Angelika M. Burger, Marina Ziche, and Giovanni Melillo
Précis: Results define off-target effects of a bioactive component of an early-phase clinical agent that may explain the anticancer effects of this agent.
- 6849 **SG2285, a Novel C2-Aryl-Substituted Pyrrolobenzodiazepine Dimer Prodrug That Cross-links DNA and Exerts Highly Potent Antitumor Activity**
John A. Hartley, Anzu Hamaguchi, Marissa Coffils, Christopher R.H. Martin, Marie Suggitt, Zhizhi Chen, Stephen J. Gregson, Luke A. Masterson, Arnaud C. Tiberghien, Janet M. Hartley, Christopher Pepper, Thet Thet Lin, Christopher Fegan, David E. Thurston, and Philip W. Howard
Précis: A cytotoxic pyrrolobenzodiazepine derivative in clinical trials is rationally engineered to a highly effective second generation pro-drug with improved DNA cross-linking activity and antitumor potency.
- 6859 **Cocarcinogenic Effect of Capsaicin Involves Activation of EGFR Signaling but Not TRPV1**
Mun Kyung Hwang, Ann M. Bode, Sanguine Byun, Nu Ry Song, Hyong Joo Lee, Ki Won Lee, and Zigang Dong
Précis: Preclinical studies in mice raise concerns that a natural compound found in hot peppers that is used in over-the-counter topical pain remedies may affect skin cancer risk by affecting EGFR signaling.
- 6870 **γ -Secretase Inhibitors Enhance Temozolomide Treatment of Human Gliomas by Inhibiting Neurosphere Repopulation and Xenograft Recurrence**
Candace A. Gilbert, Marie-Claire Daou, Richard P. Moser, and Alonzo H. Ross
Précis: Inhibitors of the Notch signaling pathway may enhance therapy for brain tumors that are presently often resistant to treatment.
- 6880 **MET Kinase Inhibitor SGX523 Synergizes with Epidermal Growth Factor Receptor Inhibitor Erlotinib in a Hepatocyte Growth Factor-Dependent Fashion to Suppress Carcinoma Growth**
Yu-Wen Zhang, Ben Staal, Curt Essenburg, Yanli Su, Liang Kang, Rich West, Dafna Kaufman, Tom DeKoning, Bryn Eagleson, Sean G. Buchanan, and George F. Vande Woude
Précis: Anticipated targeting mechanisms for drugs such as the MET kinase inhibitor examined here must be confirmed in a valid preclinical model to establish the mechanistic rationale for a sound clinical trial.
- 6891 **ZICI Overexpression Is Oncogenic in Liposarcoma**
Elliott Brill, Ryan Gobble, Christina Angeles, Mariana Lagos-Quintana, Aimee Crago, Bernadette Laxa, Penelope DeCarolis, Lei Zhang, Cristina Antonescu, Nicholas D. Socci, Barry S. Taylor, Chris Sander, Andrew Koff, and Samuel Singer
Précis: Results define a transcription factor that is essential for liposarcoma development, with implications to improve treatment of these and other aggressive mesenchymal tumors.
- 6902 **Development of a Novel Tumor-Targeted Vascular Disrupting Agent Activated by Membrane-Type Matrix Metalloproteinases**
Jennifer M. Atkinson, Robert A. Falconer, Dylan R. Edwards, Caroline J. Pennington, Catherine S. Siller, Steven D. Shnyder, Michael C. Bibby, Laurence H. Patterson, Paul M. Loadman, and Jason H. Gill
Précis: A novel tumor targeting principle is described which may help realize the potential of vascular disrupting agents to selectively and effectively trigger tumor regression.

6913 **Cutaneous Papillomavirus E6 Proteins Must Interact with p300 and Block p53-Mediated Apoptosis for Cellular Immortalization and Tumorigenesis**
 Peter Muench, Sonja Probst, Johanna Schuetz, Natalie Leiprecht, Martin Busch, Sebastian Wesselborg, Frank Stubenrauch, and Thomas Iftner

Précis: Findings offer key new mechanistic insights into how cutaneous papillomavirus infections can promote cellular immortalization and tumorigenesis.

6925 **miR-335 Directly Targets Rb1 (pRb/p105) in a Proximal Connection to p53-Dependent Stress Response**
 Michele Scarola, Stefan Schoeftner, Claudio Schneider, and Roberta Benetti

Précis: Study defines an miRNA that coordinates the action of the p53 and Rb tumor suppressor pathways, acting to enforce the operation of the p53 pathway after DNA damage.

6934 **DNA Methylation Analysis Determines the High Frequency of Genic Hypomethylation and Low Frequency of Hypermethylation Events in Plasma Cell Tumors**
 Bodour Salhia, Angela Baker, Gregory Ahmann, Daniel Auclair, Rafael Fonseca, and John Carpten

Précis: Global hypomethylation of CpG dinucleotides in gene coding regions act as an early mechanism associated with progression of multiple myeloma, with possible implications for improving treatment of this aggressive disease.

6945 **Reciprocal Activation of Prostate Cancer Cells and Cancer-Associated Fibroblasts Stimulates Epithelial-Mesenchymal Transition and Cancer Stemness**
 Elisa Giannoni, Francesca Bianchini, Lorenzo Masieri, Sergio Serni, Eugenio Torre, Lido Calorini, and Paola Chiarugi

Précis: Paracrine interactions in the tumor microenvironment facilitate EMT-mediated cancer stem cell properties that promote tumor aggressiveness and metastatic spread.

6957 **Voltage-Gated Na⁺ Channel SCN5A Is a Key Regulator of a Gene Transcriptional Network That Controls Colon Cancer Invasion**
 Carrie D. House, Charles J. Vaske, Arnold M. Schwartz, Vincent Obias, Bryan Frank, Truong Luu, Narine Sarvazyan, Rosalyn Irby, Robert L. Strausberg, Tim G. Hales, Joshua M. Stuart, and Norman H. Lee

Précis: Certain ion channel isotypes expressed on the surface of metastatic cancer cells may represent tractable new theranostic molecules for study.

6968 **Chromatin Remodeling Is Required for Gene Reactivation after Decitabine-Mediated DNA Hypomethylation**
 Jiali Si, Yanis A. Boumber, Jingmin Shu, Taichun Qin, Saira Ahmed, Rong He, Jaroslav Jelinek, and Jean-Pierre J. Issa

Précis: Findings indicate that resetting chromatin to an active state after treatment with a DNA hypomethylating drug is the key to optimize use of this drug in the clinic.

6978 **Matrix Metalloproteinase-9 Is Upregulated in Nucleophosmin-Anaplastic Lymphoma Kinase-Positive Anaplastic Lymphomas and Activated at the Cell Surface by the Chaperone Heat Shock Protein 90 to Promote Cell Invasion**
 Frédéric Lagarrigue, Sophie Dupuis-Coronas, Damien Ramel, Georges Delsol, Hélène Tronchère, Bernard Payraestre, and Frédérique Gaits-Iacovoni

Précis: Findings describe a membrane-associated complex on the surface of ALK(+) lymphomas that activates invadopodia and drives cancer cell invasion.

6988 **Matrix Metalloproteinase-9 Regulates Tumor Cell Invasion through Cleavage of Protease Nexin-1**
 Danmei Xu, Chad M. McKee, Yunhong Cao, Yunchuan Ding, Benedikt M. Kessler, and Ruth J. Muschel

Précis: Findings identify a molecular pathway that is essential for tumor cell movement driven by MMP-9, an extracellular protease that is upregulated in many types of invasive tumors.

6999 | **Suppression of Casein Kinase 1 α in Melanoma Cells Induces a Switch in β -Catenin Signaling to Promote Metastasis**
Tobias Sinnberg, Moritz Menzel, Susanne Kaesler, Tilo Biedermann, Birgit Sauer, Sven Nahnsen, Michael Schwarz, Claus Garbe, and Birgit Schitteck

Précis: Findings define a novel tumor suppressor function in melanoma, the attenuation of which stimulates beta-catenin signaling and malignant progression.

7010 | **Insulin Receptor A and IGF-1R in AML – Response**
Andrea E. Wahner Hendrickson, Paul Haluska, Charles Erlichman, Marco Gottardis, Joan M. Carboni, Judith E. Karp, and Scott H. Kaufmann

CORRECTION

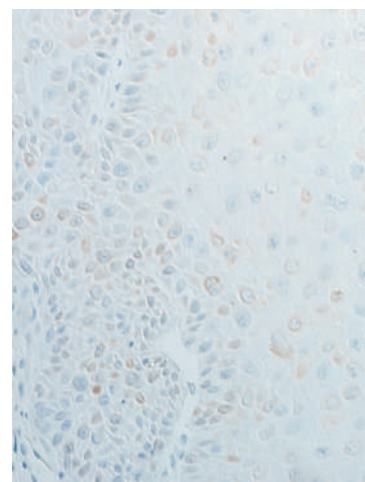
7012 | **Correction: 14-3-3 Binding Sites in the Snail Protein Are Essential for Snail-Mediated Transcriptional Repression and Epithelial-Mesenchymal Differentiation**

LETTERS TO THE EDITOR

7010 | **Insulin Receptor A and IGF-1R in AML – Letter**
Nicolas Chapuis, Catherine Lacombe, Jerome Tamburini, Didier Bouscary, and Patrick Mayeux

ABOUT THE COVER

Capsaicin is a principal pungent ingredient in hot peppers, which are consumed worldwide. Capsaicin has been shown to induce cancer cell death, and it has also been suggested that capsaicin may act as a carcinogen or cocarcinogen during the promotion stage of cancer. Hwang and colleagues show that capsaicin has a cocarcinogenic effect on TPA-promoted skin carcinogenesis *in vivo* that is mediated through the epidermal growth factor receptor (EGFR) and not the transient receptor potential vanilloid subfamily member 1 (TRPV1). Significantly, topical application of capsaicin on the dorsal skin of wild-type or TRPV1 knockout mice induced more and larger skin tumors in the knockout mice, suggesting that capsaicin acts through a TRPV1-independent mechanism. Notably, cyclooxygenase-2 (COX-2) expression was highly elevated with capsaicin treatment in TRPV1 knockout mice, and inhibitors of EGFR/MEK signaling suppressed capsaicin/TPA-induced COX-2 expression. These results raise concerns that a natural compound found in hot peppers used in over-the-counter topical pain remedies may heighten skin cancer risk by affecting EGFR-dependent signaling. For details, see the article by Hwang and colleagues on page 6859 of this issue.



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