

BREAKING ADVANCES

- 3435 | **Highlights from Recent Cancer Literature**

REVIEW

- 3437 | **Systemic DNA Damage Related to Cancer**
Olga A. Martin, Christophe E. Redon, Asako J. Nakamura, Jennifer S. Dickey, Alexandros G. Georgakilas, and William M. Bonner

MEETING REPORT

- 3442 | **National Cancer Institute Prostate Cancer Genetics Workshop**
William J. Catalona, Joan E. Bailey-Wilson, Nicola J. Camp, Stephen J. Chanock, Kathleen A. Cooney, Douglas F. Easton, Rosalind A. Eeles, Liesel M. FitzGerald, Matthew L. Freedman, Julius Gudmundsson, Rick A. Kittles, Elliott H. Margulies, Barry B. McGuire, Elaine A. Ostrander, Timothy R. Rebbeck, Janet L. Stanford, Stephen N. Thibodeau, John S. Witte, and William B. Isaacs

PRIORITY REPORTS

- 3447 | **Paradoxical Relationship between Chromosomal Instability and Survival Outcome in Cancer**
Nicolai J. Birkbak, Aron C. Eklund, Qiyuan Li, Sarah E. McClelland, David Endesfelder, Patrick Tan, Iain B. Tan, Andrea L. Richardson, Zoltan Szallasi, and Charles Swanton
- Précis:* The findings of this study reveal that high levels of chromosomal instability can be associated with improved survival in some types of cancer.
- 3453 | **Pancreatic Stellate Cells Radioprotect Pancreatic Cancer Cells through β 1-Integrin Signaling**
Tine S. Mantoni, Serena Lunardi, Osama Al-Assar, Atsushi Masamune, and Thomas B. Brunner
- Précis:* Elucidating mechanisms of radioresistance mediated by pancreatic stellate cells suggests new strategies to enhance radiotherapy for pancreatic cancer in clinic.

INTEGRATED SYSTEMS AND TECHNOLOGIES

- 3459 | **Role for Stromal Heterogeneity in Prostate Tumorigenesis**
Maria A. Kiskowski, Roger S. Jackson, Jheelam Banerjee, Xiaohong Li, Minchul Kang, Juan M. Iturregui, Omar E. Franco, Simon W. Hayward, and Neil A. Bhowmick
- Précis:* Heterogeneity of stromal TGF- β responsiveness supports cooperative intrastromal signaling and prostate adenocarcinoma progression.
- 3471 | **Functional Synergies yet Distinct Modulators Affected by Genetic Alterations in Common Human Cancers**
Marina Bessarabova, Olga Pustovalova, Weiwei Shi, Tatiana Serebriyskaya, Alex Ishkin, Kornelia Polyak, Victor E. Velculescu, Tatiana Nikolskaya, and Yuri Nikolsky
- Précis:* This genetic bioinformatics study reports the development of a cancer model offering a unified perspective on the complex signaling and regulatory networks that comprise different human cancers.

MICROENVIRONMENT AND IMMUNOLOGY

- 3482 | **Endoglin Regulates Cancer–Stromal Cell Interactions in Prostate Tumors**
Diana Romero, Christine O'Neill, Aleksandra Terzic, Liangru Contois, Kira Young, Barbara A. Conley, Raymond C. Bergan, Peter C. Brooks, and Calvin P.H. Vary
- Précis:* Findings show how a TGF- β accessory receptor being explored as a therapeutic target acts to support the viability of cancer-associated fibroblasts in the tumor microenvironment, which are key drivers of angiogenesis and growth.
- 3494 | **Expression of Id-1 Is Regulated by MCAM/MUC18: A Missing Link in Melanoma Progression**
Maya Zigler, Gabriel J. Villares, Andrey S. Dobroff, Hua Wang, Li Huang, Russell R. Braeuer, Takafumi Kamiya, Vladislava O. Melnikova, Renduo Song, Ran Friedman, Rhoda M. Alani, and Menashe Bar-Eli
- Précis:* Mechanistic findings reveal how an important cell adhesion molecule melanoma regulates metastatic progression.

3505

Tumor-Evoked Regulatory B Cells Promote Breast Cancer Metastasis by Converting Resting CD4⁺ T Cells to T-Regulatory Cells

Purevdorj B. Olkhanud, Bazarragchaa Damdinsuren, Monica Bodogai, Ronald E. Gress, Ranjan Sen, Katarzyna Wejksza, Enkhzol Malchinkhuu, Robert P. Wersto, and Arya Biragyn

Précis: Findings indicate that tumor-evoked regulatory B cells are crucial for lung metastasis, acting to convert resting T cells to regulatory T cells that promote immune escape in the target tissue.

3516

Reprogramming CD19-Specific T Cells with IL-21 Signaling Can Improve Adoptive Immunotherapy of B-Lineage Malignancies

Harjeet Singh, Matthew J. Figliola, Margaret J. Dawson, Helen Huls, Simon Olivares, Kirsten Switzer, Tiejuan Mi, Sourindra Maiti, Partow Kebriaei, Dean A. Lee, Richard E. Champlin, and Laurence J.N. Cooper

Précis: Findings reveal that addition of IL-21 to culture provides an extrinsic reprogramming signal to generate effective T-cell immunotherapy.

3528

Unraveling Cancer Chemoimmunotherapy Mechanisms by Gene and Protein Expression Profiling of Responses to Cyclophosphamide

Federica Moschella, Mara Valentini, Eleonora Aricò, Iole Macchia, Paola Sestili, Maria Teresa D'Urso, Cristiano Alessandri, Filippo Belardelli, and Enrico Proietti

Précis: Rapidly growing interest in combined regimens of chemoimmunotherapy is based upon emerging evidence that the efficacy of certain chemotherapeutic agents relies upon coordinate immune stimulatory effects.

3540

Anti-TIM3 Antibody Promotes T Cell IFN- γ -Mediated Antitumor Immunity and Suppresses Established Tumors

Shin Foong Ngiow, Bianca von Scheidt, Hisaya Akiba, Hideo Yagita, Michele W. L. Teng, and Mark J. Smyth

Précis: The first antibody targeting investigations for a little studied T-cell co-inhibitory receptor establish single agent activity and mechanism of action in multiple preclinical mouse models of cancer and primary carcinogenesis.

MOLECULAR AND CELLULAR PATHOBIOLOGY

3552

miR-125b Is Methylated and Functions as a Tumor Suppressor by Regulating the ETS1 Proto-oncogene in Human Invasive Breast Cancer

Yan Zhang, Li-Xu Yan, Qi-Nian Wu, Zi-Ming Du, Jing Chen, Ding-Zhun Liao, Ma-Yan Huang, Jing-Hui Hou, Qiu-Liang Wu, Mu-Sheng Zeng, Wen-Lin Huang, Yi-Xin Zeng, and Jian-Yong Shao

Précis: This study identifies an oncogenic transcription factor as a key target of a tumor suppressive microRNA that is downregulated in various types of invasive cancer, including breast cancer.

3563

Human Glioma Growth Is Controlled by MicroRNA-10b

Galina Gabriely, Ming Yi, Ravi S. Narayan, Johanna M. Niers, Thomas Wurdinger, Jaime Imitola, Keith L. Ligon, Santosh Kesari, Christine Esau, Robert M. Stephens, Bakhos A. Tannous, and Anna M. Krichevsky

Précis: Findings characterize the oncogenic functions of microRNA-10b in glioma biology by in silico, in vitro and in vivo approaches.

PREVENTION AND EPIDEMIOLOGY

3573

Increased Survival following Tumorigenesis in Ts65Dn Mice that Model Down Syndrome

Annan Yang and Roger H. Reeves

Précis: Mouse model studies offer compelling biological evidence that trisomy in Down Syndrome is protective against cancer, extending survival through multiple mechanisms.

3582

Evidence That Serum Levels of the Soluble Receptor for Advanced Glycation End Products Are Inversely Associated with Pancreatic Cancer Risk: A Prospective Study

Li Jiao, Stephanie J. Weinstein, Demetrius Albanes, Philip R. Taylor, Barry I. Graubard, Jarmo Virtamo, and Rachael Z. Stolzenberg-Solomon

Précis: This prospective study suggests that soluble forms of the receptor for advanced glycation end-products, a molecule with anti-inflammatory properties, might prevent pancreatic cancers thought to be driven by proinflammatory stimuli.

- 3590 **Bcl-2 Inhibits Nuclear Homologous Recombination by Localizing BRCA1 to the Endomembranes**
Corentin Laulier, Aurélie Barascu, Josée Guirouilh-Barbat, Gaëlle Pennarun, Catherine Le Chalony, François Chevalier, Gaëlle Palierno, Pascale Bertrand, Jean Marc Verbavatz, and Bernard S. Lopez
Précis: Findings suggest a new tumor suppressor function and new mode of regulation for BRCA1, with general implications for understanding the role of homologous recombination in the maintenance of genome stability.
- 3603 **Deciphering the Molecular Events Necessary for Synergistic Tumor Cell Apoptosis Mediated by the Histone Deacetylase Inhibitor Vorinostat and the BH3 Mimetic ABT-737**
Adrian P. Wiegman, Amber E. Alsop, Michael Bots, Leonie A. Cluse, Steven P. Williams, Kellie-Marie Banks, Rachael Ralli, Clare L. Scott, Anna Frenzel, Andreas Villunger, and Ricky W. Johnstone
Précis: An extensive analysis of the basis for cancer cell death synergy between two important new classes of molecular targeted therapies stimulates interest in evaluation of their clinical combination.
- 3616 **Epigenetic Silencing of MicroRNA-203 Dysregulates ABL1 Expression and Drives Helicobacter-Associated Gastric Lymphomagenesis**
Vanessa J. Craig, Sergio B. Cogliatti, Hubert Rehauer, Thomas Wündisch, and Anne Müller
Précis: Progression of *H. pylori*-associated gastritis to gastric MALT lymphoma is epigenetically regulated by promoter methylation of a microRNA that regulates the *ABL* oncogene.
- 3625 **Following Cytochrome c Release, Autophagy Is Inhibited during Chemotherapy-Induced Apoptosis by Caspase 8-Mediated Cleavage of Beclin 1**
Hua Li, Peng Wang, Quanhong Sun, Wen-Xing Ding, Xiao-Ming Yin, Robert W. Sobol, Donna B. Stolz, Jian Yu, and Lin Zhang
Précis: This study provides direct evidence that cleavage of Beclin 1 by caspases functions as a critical switch for turning off autophagy for effective killing of cancer cells.
- 3635 **The Dual EGFR/HER2 Inhibitor Lapatinib Synergistically Enhances the Antitumor Activity of the Histone Deacetylase Inhibitor Panobinostat in Colorectal Cancer Models**
Melissa J. LaBonte, Peter M. Wilson, Will Fazzino, Jared Russell, Stan G. Louie, Anthony El-Khoueiry, Heinz-Josef Lenz, and Robert D. Ladner
Précis: Findings provide a preclinical rationale to combine HDAC inhibitors with EGFR and HER2-targeted therapies in clinical trials seeking to improve colorectal cancer treatment.
- 3649 **Contribution of Abcc10 (Mrp7) to In Vivo Paclitaxel Resistance as Assessed in Abcc10^{-/-} Mice**
Elizabeth A. Hopper-Borge, Timothy Churchill, Chelsy Paulose, Emmanuelle Nicolas, Joely D. Jacobs, Olivia Ngo, Yehong Kuang, Alex Grinberg, Heiner Westphal, Zhe-Sheng Chen, Andres J. Klein-Szanto, Martin G. Belinsky, and Gary D. Kruh
Précis: This is the first study to define an ATP-binding transporter other than P-glycoprotein that mediates cytotoxic sensitivity to taxanes.
- 3658 **STAT3 Mediates Resistance to MEK Inhibitor through MicroRNA miR-17**
Bingbing Dai, Jieru Meng, Michael Peyton, Luc Girard, William G. Bornmann, Lin Ji, John D. Minna, Bingliang Fang, and Jack A. Roth
Précis: This study suggests strategies to overcome resistance to MEK kinase inhibitors which are presently being evaluated in clinical trials.
- 3669 **Differential Expression of S6K2 Dictates Tissue-Specific Requirement for S6K1 in Mediating Aberrant mTORC1 Signaling and Tumorigenesis**
Caterina Nardella, Andrea Lunardi, Giuseppe Fedele, John G. Clohessy, Andrea Alimonti, Sara C. Kozma, George Thomas, Massimo Loda, and Pier Paolo Pandolfi
Précis: Findings suggest clinical evaluation of S6 kinase inhibitors in a subset of adrenal gland tumors lacking the tumor suppressor PTEN.

3676 **Effects of Carbon Ion Beam on Putative Colon Cancer Stem Cells and Its Comparison with X-rays**

Xing Cui, Kazuhiko Oonishi, Hirohiko Tsujii, Takeshi Yasuda, Yoshitaka Matsumoto, Yoshiya Furusawa, Makoto Akashi, Tadashi Kamada, and Ryuichi Okayasu

Précis: This is the first study to show that carbon ion beam therapy may have advantages over photon beam therapy in targeting cancer stem-like cells for destruction.

3688 **ΔNp63 Versatilely Regulates a Broad NF-κB Gene Program and Promotes Squamous Epithelial Proliferation, Migration, and Inflammation**

Xinping Yang, Hai Lu, Bin Yan, Rose-Anne Romano, Yansong Bian, Jay Friedman, Praveen Duggal, Clint Allen, Ryan Chuang, Reza Ehsanian, Han Si, Satrajit Sinha, Carter Van Waes, and Zhong Chen

Précis: Mechanistic findings reveal how the interaction of two key epidermal regulatory transcription factors orchestrate inflammatory changes characteristic of injury and malignant transformation.

3701 **Does the Hepatitis B Antigen HBx Promote the Appearance of Liver Cancer Stem Cells?**

Alla Arzumanyan, Tiffany Friedman, Irene O.L. Ng, Marcia M. Clayton, Zhaorui Lian, and Mark A. Feitelson

Précis: This work establishes a link between chronic HBV infection and liver cancer by showing that the virus oncoprotein, HBx, promotes the appearance of "stemness" markers.

PHLDA1 Expression Marks the Putative Epithelial Stem Cells and Contributes to Intestinal Tumorigenesis

Anuratha Sakthianandeswaren, Michael Christie, Carla D'Andreti, Cary Tsui, Robert N. Jorissen, Shan Li, Nicholas I. Fleming, Peter Gibbs, Lara Lipton, Jordane Malatterre, Robert G. Ramsay, Toby J. Pheesse, Matthias Ernst, Rosemary E. Jeffery, Richard Poulosom, Simon J. Leedham, Stefania Segditsas, Ian P. M. Tomlinson, Oliver K. Bernhard, Richard J. Simpson, Francesca Walker, Maree C. Faux, Nicole Church, Bruno Catimel, Dustin J. Flanagan, Elizabeth Vincan, and Oliver M. Sieber

Précis: A novel marker of epithelial stem cells is suggested that functionally contributes to the migration and proliferation in colon cancer cells.

Interaction between FGFR-2, STAT5, and Progesterone Receptors in Breast Cancer

Juan P. Cerliani, Tomás Guillardoy, Sebastián Giulianelli, José P. Vaque, J. Silvio Gutkind, Silvia I. Vanzulli, Rubén Martins, Eduardo Zeitlin, Caroline A. Lamb, and Claudia Lanari

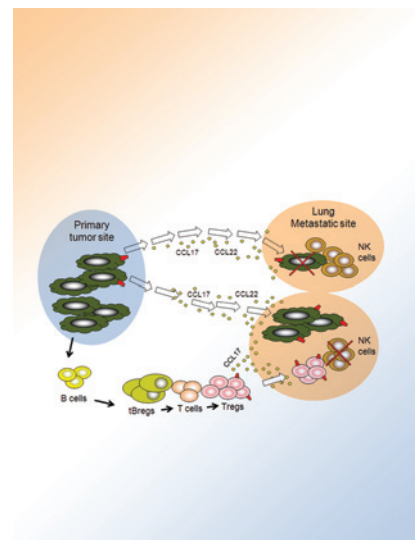
Précis: This study shows that activated nuclear FGFR-2 interact with hormone receptors and STAT5 to induce hormone related breast cancer growth.

CORRECTION

Correction: Oncogenic Synergism between ErbB1, Nucleolin, and Mutant Ras

ABOUT THE COVER

Breast cancer induces the generation of regulatory B cells (tBregs) from resting B cells. As a result, tBregs convert T cells into Tregs which infiltrate CCL17/CCL22-expressing lungs to protect metastasizing cancer cells from NK cells. For details, see the article by Olkhanud and colleagues on page 3505 of this issue.



Cancer Research

The Journal of Cancer Research (1916–1930) | The American Journal of Cancer (1931–1940)

71 (10)

Cancer Res 2011;71:3435-3732.

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