

BREAKING ADVANCES

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

REVIEWS

- 293 | **Phospholipase D Meets Wnt Signaling: A New Target for Cancer Therapy**
Dong Woo Kang, Kang-Yell Choi, and Do Sik Min
- 298 | **Physical Oncology: A Bench-to-Bedside Quantitative and Predictive Approach**
Hermann B. Frieboes, Mark A.J. Chaplain, Alastair M. Thompson, Elaine L. Bearer, John S. Lowengrub, and Vittorio Cristini

PERSPECTIVES

- 303 | **Cancer Cells Cut Homophilic Cell Adhesion Molecules and Run**
Sonya E.L. Craig and Susann M. Brady-Kalnay

MEETING REPORTS

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Evan T. Keller and Lu-Yuan Li
- 314 | **NCI Image-Guided Drug Delivery Summit**
Pushpa Tandon and Keyvan Farahani

MICROENVIRONMENT AND IMMUNOLOGY

- 318 | **Heat Shock Protein 27 Differentiates Tolerogenic Macrophages That May Support Human Breast Cancer Progression**
Sanjib Banerjee, Chuen-Fu L. Lin, Kristin A. Skinner, Linda M. Schifflauer, James Peacock, David G. Hicks, Eileen M. Redmond, David Morrow, Alissa Huston, Michelle Shayne, Howard N. Langstein, Carol L. Miller-Graziano, Jennifer Strickland, Lauren O'Donoghue, and Asit K. De
- Précis: Findings define a novel immune escape mechanism supporting breast cancer growth which is mediated by a heat shock chaperone protein.*

- 328 | **Minimal Engagement of CD103 on Cytotoxic T Lymphocytes with an E-Cadherin-Fc Molecule Triggers Lytic Granule Polarization via a Phospholipase C γ -Dependent Pathway**
Audrey Le Floch, Abdelali Jalil, Katarzyna Franciszekiewicz, Pierre Validire, Isabelle Vergnon, and Fathia Mami-Chouaib

Précis: This study defines a costimulatory signal for tumor-infiltrating T cells that is required along with T-cell receptor engagement to trigger cytolytic granule lysis of cancer cell targets.

MOLECULAR AND CELLULAR PATHOBIOLOGY

- 339 | **A Novel Transgenic Mouse Model of the Human Multiple Myeloma Chromosomal Translocation t(14;16)(q32;q23)**
Naoki Morito, Keigyou Yoh, Atsuko Maeda, Takako Nakano, Akiko Fujita, Manabu Kusakabe, Michito Hamada, Takashi Kudo, Kunihiro Yamagata, and Satoru Takahashi

Précis: A novel transgenic mouse model may offer an ideal system to study the pathogenesis of human multiple myeloma, an aggressive disease that remains relatively poorly managed.

- 349 | **HMGA2 Overexpression-Induced Ovarian Surface Epithelial Transformation Is Mediated Through Regulation of EMT Genes**
Jingjing Wu, Zhaojian Liu, Changshun Shao, Yaoqin Gong, Eva Hernando, Peng Lee, Masashi Narita, William Muller, Jinsong Liu, and Jian-Jun Wei

Précis: Introduction of HMGA2 overexpression in ovarian surface epithelial cells is sufficient for a tumor transformation both in vitro and in vivo through regulation of epithelial to mesenchymal transition.

- 360 | **p190RhoGEF (Rgnef) Promotes Colon Carcinoma Tumor Progression via Interaction with Focal Adhesion Kinase**
Hong-Gang Yu, Ju-Ock Nam, Nichol L. G. Miller, Isabelle Tanjoni, Colin Walsh, Lei Shi, Linda Kim, Xiao Lei Chen, Alok Tomar, Ssang-Taek Lim, and David D. Schlaepfer

Précis: Findings reveal a mechanism through which the protumorigenic gastrointestinal hormone gastrin acts to promote invadopodia formation and invasive motility of colorectal carcinoma cells.

371

The Tumor Suppressor Protein Menin Inhibits AKT Activation by Regulating Its Cellular Localization

Yan Wang, Atsushi Ozawa, Shadia Zaman, Nijaguna B. Prasad, Settara C. Chandrasekharappa, Sunita K. Agarwal, and Stephen J. Marx

Précis: Restricting membrane translocation of AKT from the cytoplasm may have important implications for endocrine cancers and possibly other cancers where AKT dysregulation often occurs.

383

Amiloride Modulates Alternative Splicing in Leukemic Cells and Resensitizes Bcr-Abi/T315I Mutant Cells to Imatinib

Wen-Hsin Chang, Ta-Chih Liu, Wen-Kuang Yang, Chien-Chih Lee, Yi-Hsiung Lin, Tsai-Yun Chen, and Jan-Gowth Chang

Précis: Findings offer a mechanistic rationale based on modulation of alternate RNA splicing for testing of a common antihypertensive drug as an adjuvant therapy in leukemia.

393

Phosphorylation of H2AX at Ser139 and a New Phosphorylation Site Ser16 by RSK2 Decreases H2AX Ubiquitination and Inhibits Cell Transformation

Feng Zhu, Tatyana A. Zykova, Cong Peng, Jishuai Zhang, Yong-Yeon Cho, Duo Zheng, Ke Yao, Wei-Ya Ma, Andy T. Y. Lau, Ann M. Bode, and Zigang Dong

Précis: Findings define a new function for histone H2AX, a marker of DNA damage response and repair, that may inform the role of its phosphorylation in oncogenesis.

404

A SP1/MIZ1/MYCN Repression Complex Recruits HDAC1 at the TRKA and p75^{NTR} Promoters and Affects Neuroblastoma Malignancy by Inhibiting the Cell Response to NGF

Nunzio Iraci, Daniel Diolaiti, Antonella Papa, Antonio Porro, Emanuele Valli, Samuele Gherardi, Steffi Herold, Martin Eilers, Roberto Bernardoni, Giuliano Della Valle, and Giovanni Perini

Précis: Findings establish a key pathway of clinical pathogenicity and aggressiveness in neuroblastoma, suggesting the use of HDAC inhibitors and nerve growth factor to treat MYCN-amplified tumors with the poorest prognosis.

PREVENTION AND EPIDEMIOLOGY

413

A Randomized Clinical Trial of the Effects of Supplemental Calcium and Vitamin D3 on Markers of Their Metabolism in Normal Mucosa of Colorectal Adenoma Patients

Thomas U. Ahearn, Marjorie L. McCullough, W. Dana Flanders, Qi Long, Eduard Sidelnikov, Veronika Fedirko, Carrie R. Daniel, Robin E. Rutherford, Aasma Shaukat, and Roberd M. Bostick

Précis: Findings offer mechanistic evidence for calcium and vitamin D₃ as chemopreventive agents against colorectal neoplasms, suggesting several modifiable, preneoplastic risk biomarkers for colorectal neoplasms.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

424

IL-6 Trans-Signaling in Formation and Progression of Malignant Ascites in Ovarian Cancer

Chi-Wen Lo, Min-Wei Chen, Michael Hsiao, Shiu-an Wang, Chi-An Chen, Sheng-Mou Hsiao, Jeng-Shou Chang, Tsung-Ching Lai, Stefan Rose-John, Min-Liang Kuo, and Lin-Hung Wei

Précis: Pathogenic effects of soluble receptor IL-6Ra in ovarian cancer might be specifically antagonized to enhance chemotherapeutic efficacy in ovarian cancer.

435

Small Molecule Inhibition of GDC-0449 Refractory Smoothed Mutants and Downstream Mechanisms of Drug Resistance

Gerrit J. P. Dijkgraaf, Bruno Aliche, Lasse Weinmann, Thomas Januario, Kristina West, Zora Modrusan, Dan Burdick, Richard Goldsmith, Kirk Robarge, Dan Sutherland, Suzie J. Scales, Stephen E. Gould, Robert L. Yauch, and Frederic J. de Sauvage

Précis: Findings suggest tactics to circumvent acquired resistance to a Hedgehog pathway inhibitor that is currently in clinical development as an anticancer treatment.

445

MEK1/2 Inhibitors AS703026 and AZD6244 May Be Potential Therapies for KRAS Mutated Colorectal Cancer That Is Resistant to EGFR Monoclonal Antibody Therapy

Juyong Yoon, Kyoung-Hwa Koo, and Kang-Yell Choi

Précis: Findings describe a drug therapy that can attack tumors with K-ras mutations that are resistant to existing EGFR specific therapies.

454

Combination Therapy with Vidaza and Entinostat Suppresses Tumor Growth and Reprograms the Epigenome in an Orthotopic Lung Cancer Model

Steven A. Belinsky, Marcie J. Grimes, Maria A. Picchi, Hugh D. Mitchell, Chris A. Stidley, Yohannes Tesfaigzi, Meghan M. Channell, Yanbin Liu, Robert A. Casero, Jr., Stephen B. Baylin, Mathew D. Reed, Carmen S. Tellez, and Thomas H. March

Précis: This study offers new insights into how epigenetic therapy may affect different tumor cell populations and impact cell differentiation through activation of polycomb marked genes and pathways implicated in development.

463

CCT241533 Is a Potent and Selective Inhibitor of CHK2 that Potentiates the Cytotoxicity of PARP Inhibitors

Victoria E. Anderson, Michael I. Walton, Paul D. Eve, Katherine J. Boxall, Laurent Antoni, John J. Caldwell, Wynne Aherne, Laurence H. Pearl, Antony W. Oliver, Ian Collins, and Michelle D. Garrett

Précis: While encouraging the concept of combining CHK2 inhibition with genotoxic anticancer drugs, this study also strongly supports the use of CHK2 inhibitors to potentiate the anticancer effects of PARP inhibitors, an exciting new modality for cancer treatment.

473

A Novel Sialyltransferase Inhibitor Suppresses FAK/Paxillin Signaling and Cancer Angiogenesis and Metastasis Pathways

Jia-Yang Chen, Yen-An Tang, Sin-Ming Huang, Hsueh-Fen Juan, Li-Wha Wu, Ying-Chieh Sun, Szu-Chi Wang, Kuan-Wei Wu, Gopula Balraj, Tzu-Ting Chang, Wen-Shan Li, Hung-Chi Cheng, and Yi-Ching Wang

Précis: Findings offer preclinical proof-of-concept that small molecule inhibitors of a glycoprotein modifying enzyme could offer a widely applicable strategy to treat advanced cancers.

484

Peptides and Aptamers Targeting HSP70: A Novel Approach for Anticancer Chemotherapy

Anne-Laure Rérole, Jessica Gobbo, Aurelie De Thonel, Elise Schmitt, Jean Paul Pais de Barros, Arlette Hammann, David Lanneau, Eric Fourmaux, Oleg Deminov, Olivier Micheau, Laurent Lagrost, Pierre Colas, Guido Kroemer, and Carmen Garrido

Précis: Lead compounds offer proof-of-concept for aptamer peptides that can exert immunogenic antitumor effects based on blockade of the central protein-folding chaperone molecule Hsp70.

496

Eribulin Induces Irreversible Mitotic Blockade: Implications of Cell-Based Pharmacodynamics for *In vivo* Efficacy under Intermittent Dosing Conditions

Murray J. Towle, Kathleen A. Salvato, Bruce F. Wels, Kimberley K. Aalfs, Wanjun Zheng, Boris M. Seletsky, Xiaojie Zhu, Bryan M. Lewis, Yoshito Kishi, Melvin J. Yu, and Bruce A. Littlefield

Précis: A mechanistically unique microtubule inhibitor in Phase III trials induces an irreversible mitotic block that contributes to its *in vivo* antitumor efficacy under intermittent dosing conditions.

506

The BH3 Mimetic ABT-737 Induces Cancer Cell Senescence

Jin H. Song, Karthikeyan Kandasamy, Marina Zemskova, Ying-Wei Lin, and Andrew S. Kraft

Précis: An important proapoptotic drug currently in human clinical trials is found to activate gene transcription, heighten DNA damage, and trigger senescence in cancer cells that are not susceptible to death induced by this agent, potentially expanding its effective use as a cancer therapy.

516

Highly Specific Auto-Antibodies against Claudin-18 Isoform 2 Induced by a Chimeric HBcAg Virus-Like Particle Vaccine Kill Tumor Cells and Inhibit the Growth of Lung Metastases

Thorsten Klamp, Jens Schumacher, Georg Huber, Christoph Kühne, Ulrich Meissner, Abderraouf Selmi, Thomas Hiller, Sebastian Kreiter, Jürgen Markl, Özlem Türecci, and Ugur Sahin

Précis: Findings describe a novel, chimeric bio-nanoparticle-based vaccine that induces auto-antibodies directed against the native conformation of a pan-cancer target and demonstrates cytotoxic and tumoricidal effector functions.

528

CaM Kinase Kinase β -Mediated Activation of the Growth Regulatory Kinase AMPK Is Required for Androgen-Dependent Migration of Prostate Cancer Cells

Daniel E. Frigo, Matthew K. Howe, Bryan M. Wittmann, Abigail M. Brunner, Ian Cushman, Qianben Wang, Myles Brown, Anthony R. Means, and Donald P. McDonnell

Précis: This study describes a pathogenic growth regulatory pathway in prostate cancer that suggests important novel targets for therapy.

538

ROS and CHOP Are Critical for Dibenzylideneacetone to Sensitize Tumor Cells to TRAIL through Induction of Death Receptors and Downregulation of Cell Survival Proteins

Sahdeo Prasad, Vivek R. Yadav, Jayaraj Ravindran, and Bharat B. Aggarwal

Précis: Drugs that can defeat resistance mechanisms to TRAIL may improve opportunities to exploit the anticancer properties of this cytokine.

583

microRNA-616 Induces Androgen-Independent Growth of Prostate Cancer Cells by Suppressing Expression of Tissue Factor Pathway Inhibitor TFPI-2

Stephanie Ma, Yuen Piu Chan, Pak Shing Kwan, Terence K. Lee, Mingxia Yan, Kwan Ho Tang, Ming Tat Ling, Juergen R. Vielkind, Xin-Yuan Guan, and Kwok Wah Chan

Précis: Findings reveal an interesting microRNA-regulated extracellular tumor suppressor pathway that is critical to support androgen-independent prostate cancers and amenable to therapeutic disruption.

TUMOR AND STEM CELL BIOLOGY

550

Microfluidic-Based Multiplex qRT-PCR Identifies Diagnostic and Prognostic microRNA Signatures in the Sera of Prostate Cancer Patients

Felix Moltzahn, Adam B. Olshen, Lauren Baehner, Andrew Peek, Lawrence Fong, Hubert Stöppler, Jeffrey Simko, Joan F. Hilton, Peter Carroll, and Robert Blleloch

Précis: MicroRNA signatures that can be detected in blood serum may allow definition of different risk-stratified patients with prostate cancer.

561

Chromosome Breakage Is Regulated by the Interaction of the BLM Helicase and Topoisomerase II α

Beatriz Russell, Saumitri Bhattacharyya, Jeremy Keirse, April Sandy, Patrick Grierson, Erin Perchiniak, Juraj Kavecansky, Samir Acharya, and Joanna Groden

Précis: Results elucidate a DNA repair mechanism that is critical to maintain chromosome stability in cells, a deficiency which greatly increases cancer risk.

572

Decreased Expression and Androgen Regulation of the Tumor Suppressor Gene INPP4B in Prostate Cancer

Myles C. Hodgson, Long-jiang Shao, Anna Frolov, Rile Li, Leif E. Peterson, Gustavo Ayala, Michael M. Ittmann, Nancy L. Weigel, and Irina U. Agoulnik

Précis: Findings strongly reinforce the concept that therapeutics which target Akt signaling are likely to be effective in blocking the growth of metastatic prostate cancer cells.

593

Suppression of Colonic Polyposis by Homeoprotein CDX2 through its Nontranscriptional Function that Stabilizes p27^{Kip1}

Koji Aoki, Fumihiko Kakizaki, Hiromi Sakashita, Toshiaki Manabe, Masahiro Aoki, and Makoto M. Taketo

Précis: A novel nontranscriptional function of CDX2 plays a key role in tumor suppression through stabilization of p27Kip1.

603

Cytokine Receptor CXCR4 Mediates Estrogen-Independent Tumorigenesis, Metastasis, and Resistance to Endocrine Therapy in Human Breast Cancer

Lyndsay V. Rhodes, Sarah P. Short, Nicole F. Neel, Virgilio A. Salvo, Yun Zhu, Steven Elliott, Yongkun Wei, Dihua Yu, Menghong Sun, Shannon E. Muir, Juan P. Fonseca, Melyssa R. Bratton, Chris Segar, Syreeta L. Tilghman, Tammy Sobolik-Delmaire, Linda W. Horton, Snjezana Zaja-Milatovic, Bridgette M. Collins-Burow, Scott Wadsworth, Barbara S. Beckman, Charles E. Wood, Suzanne A. Fuqua, Kenneth P. Nephew, Paul Dent, Rebecca A. Worthylake, Tyler J. Curiel, Mien-Chie Hung, Ann Richmond, and Matthew E. Burow

Précis: Findings describe a potentially important mechanism of resistance to endocrine therapies used widely in nearly all ER+ breast cancer patients, with implications on how to bypass this resistance mechanism.

614

Breast Cancer Stem Cells Are Regulated by Mesenchymal Stem Cells through Cytokine Networks

Suling Liu, Christophe Ginestier, Sing J. Ou, Shawn G. Clouthier, Shivani H. Patel, Florence Monville, Hasan Korkaya, Amber Heath, Julie Dutcher, Celina G. Kleer, Younghun Jung, Gabriela Dontu, Russell Taichman, and Max S. Wicha

Précis: Strategies aimed at interfering with the proposed cytokine loops may provide a means of targeting the cancer stem cell population.

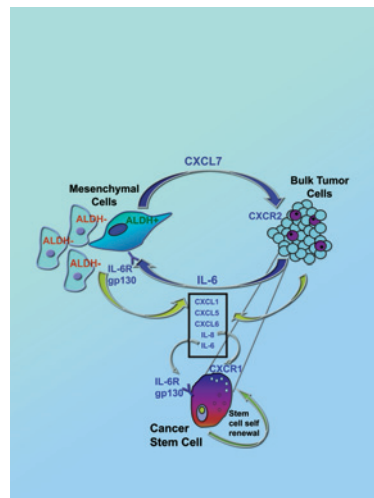
**Statistical Design Considerations in
Animal Studies Published Recently in
Cancer Research**

Kenneth R. Hess

**Correction: Surface-Immobilized
Aptamers for Cancer Cell Isolation and
Microscopic Cytology**

ABOUT THE COVER

Breast cancer stem cells are regulated by mesenchymal stem cells via cytokine networks. Breast cancer cells secrete IL6, which recruits bone marrow-derived mesenchymal stem cells and induces CXCL7 secretion by these cells. CXCL7 in turn induces the production of multiple cytokines including IL8 and IL6, which completes a positive feedback loop and stimulates the self-renewal of breast cancer stem cells driving tumor growth and metastasis. For details, see the article by Liu and colleagues on page 614 of this issue.



Cancer Research

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