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5606 **TGF-β/SMAD/GLI2 Signaling Axis in Cancer Progression and Metastasis**
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5616 **The First AACR Special Conference on Stem Cells, Development, and Cancer: Some of These Cells Are Not Like the Others**
David G. Kent, Jennifer C. Lin, and Geraldine Aubert

PRIORITY REPORT

5621 **HERC2 Interacts with Claspin and Regulates DNA Origin Firing and Replication Fork Progression**
Naoki Izawa, Wenwen Wu, Ko Sato, Hiroyuki Nishikawa, Akihiro Kato, Narikazu Boku, Fumio Itoh, and Tomohiko Ohta

Précis: *An E3 ubiquitin ligase that targets the BRCA1 breast tumor suppressor for degradation also participates in DNA replication, possibly playing a role in breast carcinogenesis through this mechanism.*

CLINICAL STUDIES

5626 **Phase I Study of PARP Inhibitor ABT-888 in Combination with Topotecan in Adults with Refractory Solid Tumors and Lymphomas**
Shivaani Kummar, Alice Chen, Jiuping Ji, Yiping Zhang, Joel M. Reid, Matthew Ames, Lee Jia, Marcie Weil, Giovanna Speranza, Anthony J. Murgo, Robert Kinders, Lihua Wang, Ralph E. Parchment, John Carter, Howard Stotler, Larry Rubinstein, Melinda Hollingshead, Giovanni Melillo, Yves Pommier, William Bonner, Joseph E. Tomaszewski, and James H. Doroshow

Précis: *Results of this clinical trial confirm anticipations that an exciting new class of PARP inhibitors developed for cancer treatment can indeed modulate the capacity to repair topoisomerase I–mediated DNA damage in humans, as predicted by preclinical studies.*

INTEGRATED SYSTEMS AND TECHNOLOGIES

5635 **microRNA-Associated Progression Pathways and Potential Therapeutic Targets Identified by Integrated mRNA and microRNA Expression Profiling in Breast Cancer**
Francesca M. Buffa, Carme Camps, Laura Winchester, Cameron E. Snell, Harriet E. Gee, Helen Sheldon, Marian Taylor, Adrian L. Harris, and Jiannis Ragoussis

Précis: *This study introduces and utilizes an integrated profiling approach to establish an association between microRNA expression, progression, and prognosis in cancer.*

5646 **Genome-wide Profiling of Chromatin Signatures Reveals Epigenetic Regulation of MicroRNA Genes in Colorectal Cancer**
Hiromu Suzuki, Shintaro Takatsuka, Hirofumi Akashi, Eiichiro Yamamoto, Masanori Nojima, Reo Maruyama, Masahiro Kai, Hiro-o Yamano, Yasushi Sasaki, Takashi Tokino, Yasuhisa Shinomura, Kohzoh Imai, and Minoru Toyota

Précis: *Results reveal how chromatin signatures and miRNA dysregulation are connected in colorectal cancer and suggest that miRNA reexpression may contribute to the effects of epigenetic therapy.*

5659 **Small RNA Sequencing and Functional Characterization Reveals MicroRNA-143 Tumor Suppressor Activity in Liposarcoma**
Stacy Ugras, Elliott Brill, Anders Jacobsen, Markus Hafner, Nicholas D. Socci, Penelope L. DeCarolis, Raya Khanin, Rachael O'Connor, Aleksandra Mihailovic, Barry S. Taylor, Robert Sheridan, Jeffrey M. Gimble, Agnes Viale, Aimee Crago, Cristina R. Antonescu, Chris Sander, Thomas Tuschl, and Samuel Singer

Précis: *A microRNA that inhibits cytokinesis acts as a tumor suppressor in liposarcoma, where restoration of its function or targets may offer therapeutic utility in this poorly managed cancer.*

MICROENVIRONMENT AND IMMUNOLOGY

5670 **Localization and Density of Immune Cells in the Invasive Margin of Human Colorectal Cancer Liver Metastases Are Prognostic for Response to Chemotherapy**
Niels Halama, Sara Michel, Matthias Kloor, Inka Zoernig, Axel Benner, Anna Spille, Thora Pommerencke, Magnus von Knebel Doeberitz, Gunnar Folprecht, Birgit Luber, Nadine Feyen, Uwe M. Martens, Philipp Beckhove, Sacha Gnjatic, Peter Schirmacher, Esther Herpel, Juergen Weitz, Niels Grabe, and Dirk Jaeger

Précis: *Increasing evidence supports the concept that the interaction between a colorectal tumor and its local immune microenvironment dictates patient prognosis and treatment response.*

5678 **Human Solid Tumors Contain High Endothelial Venules: Association with T- and B-Lymphocyte Infiltration and Favorable Prognosis in Breast Cancer**
Ludovic Martinet, Ignacio Garrido, Thomas Filleron, Sophie Le Guellec, Elisabeth Bellard, Jean-Jacques Fournie, Philippe Rochaix, and Jean-Philippe Girard

Précis: *This study shows that human solid tumors often contain a class of blood vessels that are characteristic of lymph nodes and other lymphoid tissues, revealing a kind of nodal mimicry in the tumor microenvironment that promotes lymphocyte entry and affects prognosis.*

5688 **Targeted Therapeutic Remodeling of the Tumor Microenvironment Improves an HER-2 DNA Vaccine and Prevents Recurrence in a Murine Breast Cancer Model**
Debbie Liao, Ze Liu, Wolfgang J. Wrasidlo, Yunping Luo, Giang Nguyen, Tingmei Chen, Rong Xiang, and Ralph A. Reisfeld

Précis: *Findings strengthen the concept that a direct therapeutic inhibition of Stat3 in the tumor immune microenvironment is sufficient to improve the efficacy of cancer immunotherapy.*

5697 **IL-12 Release by Engineered T Cells Expressing Chimeric Antigen Receptors Can Effectively Muster an Antigen-Independent Macrophage Response on Tumor Cells That Have Shut Down Tumor Antigen Expression**
Markus Chmielewski, Caroline Kopecky, Andreas A. Hombach, and Hinrich Abken

Précis: *This study shows how engineering IL-12 expression as part of a new type of adoptive T-cell therapy can recruit macrophages into an antitumor response, rendering it more effective against tumors that are escaping immunity by shutting down expression of tumor antigens.*

5707 **CXCR3 Enhances a T-Cell–Dependent Epidermal Proliferative Response and Promotes Skin Tumorigenesis**
Ashley E. Winkler, Joshua J. Brotman, Meredith E. Pittman, Nancy P. Judd, James S. Lewis, JrRobert D. Schreiber, and Ravindra Uppaluri

Précis: *This genetic study challenges the view that CXCR3 restricts cancer development, finding instead that this chemokine receptor likely promotes tumorigenesis through a T cell–dependent induction of keratinocyte proliferation.*

MOLECULAR AND CELLULAR PATHOBIOLOGY

5717 **Angiopoietin-1 and -2 Exert Antagonistic Functions in Tumor Angiogenesis, yet Both Induce Lymphangiogenesis**
Ernesta Fagiani, Pascal Lorentz, Lucie Kopfstein, and Gerhard Christofori

Précis: *Findings assess the functional contribution of Angiopoietin family members to tumor angiogenesis and suggest that it is their relative ratio that guides vascular growth.*

5728 **Dual Function of ERRα in Breast Cancer and Bone Metastasis Formation: Implication of VEGF and Osteoprotegerin**
Anaïs Fradet, Helène Sorel, Lamia Bouazza, Delphine Goehrig, Baptiste Dépalle, Akeila Bellahcène, Vincent Castronovo, Hélène Follet, Françoise Descotes, Jane E. Aubin, Philippe Clézardin, and Edith Bonnelye

Précis: *Findings identify a prognostic factor in breast cancer that predicts increased local growth and invasion in the primary tumor, but decreased osteolytic lesions in bone.*

5739 **Estrogen-Dependent Gene Transcription in Human Breast Cancer Cells Relies upon Proteasome-Dependent Monoubiquitination of Histone H2B**
Tanja Prenzel, Yvonne Begus-Nahrmann, Frank Kramer, Magali Hennion, Chieh Hsu, Theresa Gorsler, Corinna Hintermair, Dirk Eick, Elisabeth Kremmer, Mikael Simons, Tim Beissbarth, and Steven A. Johnsen

Précis: *This study offers a mechanistic rationale to exploit the proteasome inhibitor bortezomib for treatment of ER+ breast cancers, based on learning how it indirectly blocks the ability of the estrogen receptor to induce its downstream target genes.*

5754 **Insulin Increases *De Novo* Steroidogenesis in Prostate Cancer Cells**
Amy A. Lubik, Jennifer H. Gunter, Stephen C. Hendy, Jennifer A. Locke, Hans H. Adomat, Vanessa Thompson, Adrian Herington, Martin E. Gleave, Michael Pollak, and Colleen C. Nelson

Précis: *Elevated insulin levels associated with androgen deprivation treatments for prostate cancer may exacerbate subsequent progression in part by inducing compensatory alternate pathways for androgen synthesis.*

5765 **The Tumor Suppressive MicroRNA *miR-218* Targets the mTOR Component *Rictor* and Inhibits AKT Phosphorylation in Oral Cancer**
Atsushi Uesugi, Ken-ichi Kozaki, Tomohiko Tsuruta, Mayuko Furuta, Kei-ichi Morita, Issei Imoto, Ken Omura, and Johji Inazawa

Précis: *This study offers an important advance in improving understanding and potential treatment for oral squamous carcinomas that are poorly managed but rising rapidly in incidence.*

5779 **Identification of *Fat4* and *Tsc22d1* as Novel Candidate Genes for Spontaneous Pulmonary Adenomas**
Annerose Berndt, Clinton L. Cario, Kathleen A. Silva, Victoria E. Kennedy, David E. Harrison, Beverly Paigen, and John P. Sundberg

Précis: *Genome wide association studies used to compare the incidence of spontaneous lung adenoma in 28 strains of mice suggest major differences in males and females, with potential implications for understanding human susceptibilities to lung cancer.*

PREVENTION AND EPIDEMIOLOGY

5792 **Modification of *BRCA1*-Associated Breast and Ovarian Cancer Risk by *BRCA1*-Interacting Genes**
Timothy R. Rebbeck, Nandita Mitra, Susan M. Domchek, Fei Wan, Tara M. Friebel, Teo V. Tran, Christian F. Singer, Muy-Kheng Maria Tea, Joanne L. Blum, Nadine Tung, Olufunmilayo I. Olopade, Jeffrey N. Weitzel, Henry T. Lynch, Carrie L. Snyder, Judy E. Garber, Antonis C. Antoniou, Susan Peock, D. Gareth Evans, Joan Paterson, M. John Kennedy, Alan Donaldson, Huw Dorkins, Douglas F. Easton for the Epidemiological Study of *BRCA1* and *BRCA2* Mutation Carriers (EMBRACE), Wendy S. Rubinstein, Mary B. Daly, Claudine Isaacs, Heli Nevanlinna, Fergus J. Couch, Irene L. Andrulis, Eitan Freidman, Yael Laitman, Patricia A. Ganz, Gail E. Tomlinson, Susan L. Neuhausen, Steven A. Narod, Catherine M. Phelan, Roger Greenberg, and Katherine L. Nathanson

Précis: *This study offers an explanation for why women with BRCA1 mutations differ in their risks of breast and ovarian cancer, based on genetic variations in BRCA1-interacting factors.*

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

5806 **Modulating Microtubule Stability Enhances the Cytotoxic Response of Cancer Cells to Paclitaxel**
Ahmed Ashour Ahmed, Xiaoyan Wang, Zhen Lu, Juliet Goldsmith, Xiao-Feng Le, Geoffrey Grandjean, Geoffrey Bartholomeusz, Bradley Broom, and Robert C. Bast Jr

Précis: *This study created a rational cell-based strategy to identify targeted therapeutics, including existing kinase inhibitors, that could be used to enhance the therapeutic effects of the widely used chemotherapeutic drug paclitaxel.*

5818 **STK33 Kinase Activity Is Nonessential in KRAS-Dependent Cancer Cells**
Carol Babij, Yihong Zhang, Robert J. Kurzeja, Anke Munzli, Amro Shehabeldin, Manory Fernando, Kim Quon, Paul D. Kassner, Astrid A. Ruefli-Brasse, Vivienne J. Watson, Flordeliza Fajardo, Angela Jackson, James Zondlo, Yu Sun, Aaron R. Ellison, Cherylene A. Plewa, Tisha San Miguel, John Robinson, John McCarter, Ralf Schwandner, Ted Judd, Josette Carnahan, and Isabelle Dussault

Précis: *Findings show that STK33 is not required for KRAS-dependent growth and therefore does not represent a suitable therapeutic target in KRAS-driven cancers.*

5827 **Potent Antitumor Immunity Generated by a CD40-Targeted Adenoviral Vaccine**
Basav N. Hangalapura, Dinja Oosterhoff, Jan de Groot, Louis Boon, Thomas Tüting, Alfons J. van den Eertwegh, Winald R. Gerritsen, Victor W. van Beusechem, Alexander Pereboev, David T. Curiel, Rik J. Scheper, and Tanja D. de Gruijl

Précis: *Adenovirus vectors can be engineered to deliver tumor antigens to dendritic cells* in vivo, *generating potent antitumor immunity without the need for* ex vivo *manipulations to make personalized dendritic cell vaccines for cancer treatment, such as pioneered by the recently approved prostate cancer vaccine Provenge.*

5838 **Clusterin Inhibition Using OGX-011 Synergistically Enhances Hsp90 Inhibitor Activity by Suppressing the Heat Shock Response in Castrate-Resistant Prostate Cancer**
Francois Lamoureux, Christian Thomas, Min-Jean Yin, Hidetoshi Kuruma, Eliana Beraldi, Ladan Fazli, Amina Zoubeidi, and Martin E. Gleave

Précis: *An inhibitor of the heat shock protein clusterin is shown to attenuate a cytoprotective stress response to Hsp90 inhibitors in cancer cells, thereby identifying a promising cotargeting strategy of these drugs in treating advanced cancers.*

5850 **Bcl-2 Family Genetic Profiling Reveals Microenvironment-Specific Determinants of Chemotherapeutic Response**
Justin R. Pritchard, Luke A. Gilbert, Corbin E. Meacham, Jennifer L. Ricks, Hai Jiang, Douglas A. Lauffenburger, and Michael T. Hemann

Précis: *This RNAi-based screen for Bcl-2 family dependent modifiers of chemotherapeutic responses suggests that tissue microenvironments may be responsible for conferring the major determinants of sensitivity and resistance of cancer cells.*

5859 **Overexpression of MBD2 in Glioblastoma Maintains Epigenetic Silencing and Inhibits the Antiangiogenic Function of the Tumor Suppressor Gene *BAI1***
Dan Zhu, Stephen B. Hunter, Paula M. Vertino, and Erwin G. Van Meir

Précis: *Findings elucidate an important mechanism by which epigenetic silencing may promote brain cancer, and also identify a regulator of DNA methylation as a candidate target for therapeutic intervention.*

5871 **Antitumor Activity of Metal-Chelating Compound Dp44mT Is Mediated by Formation of a Redox-Active Copper Complex That Accumulates in Lysosomes**
David B. Lovejoy, Patric J. Jansson, Ulf T. Brunk, Jacky Wong, Prem Ponka, and Des R. Richardson

Précis: *A novel generalized strategy to target cancer cells by disrupting lysosome function in a selective manner is shown to be associated with apoptosis induction and potent antitumor effects.*

5881 **Chromogranin A Restricts Drug Penetration and Limits the Ability of NGR-TNF to Enhance Chemotherapeutic Efficacy**
Eleonora Dondossola, Anna Maria Gasparri, Barbara Colombo, Angelina Sacchi, Flavio Curnis, and Angelo Corti

Précis: *Findings define a functional blood borne marker for patient responsiveness to a chemosensitizing TNF derivative being tested in clinical trials, with implications for the design and interpretation of those trials.*

5891 **Definition of the Landscape of Promoter DNA Hypomethylation in Liver Cancer**
Barbara Stefanska, Jian Huang, Bishnu Bhattacharyya, Matthew Suderman, Michael Hallett, Ze-Guang Han, and Moshe Szyf

Précis: *Findings demonstrate a central role for promoter hypomethylation in cancer growth and metastasis and suggest that targeting DNA demethylases could offer powerful therapeutic options for cancer treatment.*

5904 **Blocking Hedgehog Survival Signaling at the Level of the GLIGenes Induces DNA Damage and Extensive Cell Death in Human Colon Carcinoma Cells**
Tapati Mazumdar, Jennifer DeVecchio, Akwasi Agyeman, Ting Shi, and Janet A. Houghton

Précis: *Direct targeting of the Hedgehog signaling pathway at the transcription factor level, rather than upstream, is found to be a relatively more effective strategy to trigger cell death in human colon carcinoma cells.*

5915 **Cytotoxic Activity of Immunotoxin SS1P Is Modulated by TACE-Dependent Mesothelin Shedding**
Yujian Zhang, Oleg Chertov, Jingli Zhang, Raffit Hassan, and Ira Pastan

Précis: *This study rationalizes a general strategy to improve cancer-selective targeting by a wide variety of monoclonal antibodies, immunoconjugates, and immunotoxins used in cancer treatment.*

5923 **Development of a Hypoxia Gene Expression Classifier with Predictive Impact for Hypoxic Modification of Radiotherapy in Head and Neck Cancer**
Kasper Toustrup, Brita Singers Sørensen, Marianne Nordsmark, Morten Busk, Carsten Wiuf, Jan Alsner, and Jens Overgaard

Précis: *A novel hypoxia gene expression classifier is found to identify individuals who might benefit from hypoxic modification of radiotherapy in head and neck cancers.*

TUMOR AND STEM CELL BIOLOGY

5932 **Novel Cryo-Imaging of the Glioma Tumor Microenvironment Reveals Migration and Dispersal Pathways in Vivid Three-Dimensional Detail**
Susan M. Burden-Gulley, Mohammed Q. Qutaish, Kristin E. Sullivant, Hong Lu, Jing Wang, Sonya E.L. Craig, James P. Basilion, David L. Wilson, and Susann M. Brady-Kalnay

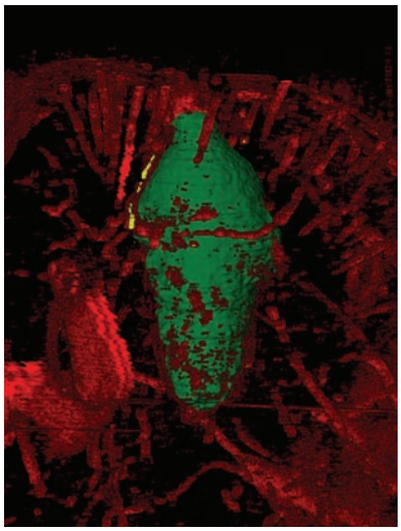
Précis: *Imaging methodologies described in this study may revolutionize the analysis of therapeutics that block cancer cell migration and dispersal in the tumor microenvironment.*

CORRECTIONS

5941 **Correction: Interaction between FGFR-2, STAT5, and Progesterone Receptors in Breast Cancer**

5942 **Correction: TGFβ/TNFα-Mediated Epithelial–Mesenchymal Transition Generates Breast Cancer Stem Cells with a Claudin-Low Phenotype**

ABOUT THE COVER



Human U-87 MG glioma tumor cells expressing green fluorescent protein were xenografted orthotopically into an athymic nude mouse brain. The mouse brain was cryo-imaged and reconstructed in 3 dimensions to show the human U-87 MG glioma main tumor mass (pseudocolored green), dispersed tumor cells (pseudocolored yellow), and the mouse brain vasculature (pseudocolored red). Cells from the U-87 MG glioma tumor (yellow cells) migrated and dispersed on a nearby blood vessel. For details, see the article by Burden-Gulley and colleagues on page 5932 of this issue.

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