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Cancer Research

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- Précis: The efficacy of hundreds of dendritic cell vaccines currently in clinical development might be improved dramatically simply by reducing the oxygen level in tumor cell cultures that are used as source of antigens to prime the vaccine.*

INTEGRATED SYSTEMS AND TECHNOLOGIES

- 6590 | **Aberrant Lipid Metabolism in Hepatocellular Carcinoma Revealed by Plasma Metabolomics and Lipid Profiling**
Andrew D. Patterson, Olivier Maurhofer, Diren Beyoğlu, Christian Lanz, Kristopher W. Krausz, Thomas Pabst, Frank J. Gonzalez, Jean-François Dufour, and Jeffrey R. Idle
- Précis: A sophisticated set of metabolomic discovery platforms were employed in this study to define plasma markers of intermediate-stage hepatocellular carcinoma, revealing a number of new molecular alterations and illustrating the potential of this technology for developing pathophysiological understanding and discovering informative diagnostics.*

MICROENVIRONMENT AND IMMUNOLOGY

- 6601 | **Antiangiogenic and Antimetastatic Activity of JAK Inhibitor AZD1480**
Hong Xin, Andreas Herrmann, Karen Reckamp, Wang Zhang, Sumanta Pal, Michael Hedvat, Chunyan Zhang, Wei Liang, Anna Scuto, Shaobu Weng, Deborah Morosini, Zhu A. Cao, Michael Zinda, Robert Figlin, Dennis Huszar, Richard Jove, and Hua Yu
- Précis: JAK inhibitors in clinical development effectively inhibit tumor angiogenesis and metastasis mediated by STAT3 in tumor stromal cells as well as tumor cells themselves, encouraging their broader evaluation for cancer treatment than only in malignancies characterized by JAK/STAT mutations.*
- 6611 | **Targeting the Immunoregulator SRA/CD204 Potentiates Specific Dendritic Cell Vaccine-Induced T-cell Response and Antitumor Immunity**
Huanfa Yi, Chunqing Guo, Xiaofei Yu, Ping Gao, Jie Qian, Daming Zuo, Masoud H. Manjili, Paul B. Fisher, John R. Subjeck, and Xiang-Yang Wang
- Précis: Findings offer a straightforward strategy to enhance the potency of dendritic cell vaccines, for which Provenge is the first FDA-approved example, by targeting a pattern recognition scavenger receptor that limits the ability of dendritic cells to restore T cell-mediated antitumor immunity.*

6621 **Human Breast Tumor Cells Induce Self-Tolerance Mechanisms to Avoid NKG2D-Mediated and DNAM-Mediated NK Cell Recognition**

Emilie Mamessier, Aude Sylvain, François Bertucci, Rémy Castellano, Pascal Finetti, Gilles Houvenaeghel, Emmanuelle Charaffe-Jaufret, Daniel Birnbaum, Alessandro Moretta, and Daniel Olive

Précis: All breast cancer subtypes develop mechanisms to escape natural killer cell-mediated immune recognition, rationalizing the development of immunotherapies that can relieve escape and/or enhance natural killer cell function.

6654 **SIRT1 Is Essential for Oncogenic Signaling by Estrogen/Estrogen Receptor α in Breast Cancer**

Selvakumar Elangovan, Sabarish Ramachandran, Narayanan Venkatesan, Sudha Ananth, Jaya P. Gnana-Prakasam, Pamela M. Martin, Darren D. Browning, Patricia V. Schoenlein, Puttur D. Prasad, Vadivel Ganapathy, and Muthusamy Thangaraju

Précis: Small molecule inhibitors of the histone deacetylase SIRT1 presently in clinical development may find an important application in potentiating the beneficial effects of antiestrogen treatments in breast cancer.

MOLECULAR AND CELLULAR PATHOBIOLOGY

6633 **HB-EGF and PDGF Mediate Reciprocal Interactions of Carcinoma Cells with Cancer-Associated Fibroblasts to Support Progression of Uterine Cervical Cancers**

Takuya Murata, Hiroto Mizushima, Ichino Chinen, Hiroki Moribe, Shigeo Yagi, Robert M. Hoffman, Tadashi Kimura, Kiyoshi Yoshino, Yutaka Ueda, Takayuki Enomoto, and Eisuke Mekada

Précis: Findings define two central drivers of the reciprocal master-slave relationship created between cancer cells and cancer-associated fibroblasts in the tumor microenvironment.

6643 **Human Cytomegalovirus US28 Found in Glioblastoma Promotes an Invasive and Angiogenic Phenotype**

Liliana Soroceanu, Lisa Matlaf, Vladimir Bezrookove, Loui Harkins, Roxanne Martinez, Mary Greene, Patricia Soteropoulos, and Charles S. Cobbs

Précis: Human cytomegalovirus infections that occur commonly in deadly brain glioblastomas may be contributing strongly to the aggressive progression which characterizes this disease, through expression of a viral G protein-like coupled receptor that can be therapeutically targeted.

6665 **Progression of Human Bronchioloalveolar Carcinoma to Invasive Adenocarcinoma Is Modeled in a Transgenic Mouse Model of K-ras-Induced Lung Cancer by Loss of the TGF- β Type II Receptor**

Alain C. Borczuk, Marieta Sole, Ping Lu, Jinli Chen, May-Lin Wilgus, Richard A. Friedman, Steven M. Albelda, and Charles A. Powell

Précis: The important new model of lung cancer progression reported in this study recapitulates the genomics and clinical progression of human lung adenocarcinoma, also highlighting its control by an important TGF- β receptor.

6676 **Plasminogen Receptor S100A10 Is Essential for the Migration of Tumor-Promoting Macrophages into Tumor Sites**

Kyle D. Phipps, Alexi P. Surette, Paul A. O'Connell, and David M. Waisman

Précis: This important study reveals a pivotal signaling node in cancer progression by demonstrating that the receptor for plasminogen, a key regulator of blood coagulation and metastasis, is essential for migration of tumor-promoting macrophages into tumor sites.

6684 **Manganese Superoxide Dismutase Is a p53-Regulated Gene That Switches Cancers between Early and Advanced Stages**

Sanjit K. Dhar, Jitbanjong Tangpong, Luksana Chaiswing, Terry D. Oberley, and Daret K. St. Clair

Précis: This study reports a novel genetic model of skin carcinogenesis that reveals the importance of a linkage between ROS scavenging networks and cellular stress responses involving p53.

6696 **A Novel MLL5 Isoform That Is Essential to Activate E6 and E7 Transcription in HPV16/18-Associated Cervical Cancers**

Chow Wenn Yew, Pei Lee, Wai Keong Chan, Vania Kai Jun Lim, Sun Kuie Tay, Theresa M.C. Tan, and Lih-Wen Deng

Précis: This study reports the discovery of a molecule exclusively expressed in HPV-associated cervical cancers, where it may offer a novel and disease selective therapeutic target and biomarker.

6708 **RNA Helicase DDX5 Is a p53-Independent Target of ARF That Participates in Ribosome Biogenesis**

Anthony J. Saporita, Hsiang-Chun Chang, Crystal L. Winkeler, Anthony J. Apicelli, Raleigh D. Kladney, Jianbo Wang, R. Reid Townsend, Loren S. Michel, and Jason D. Weber

Précis: This study offers an answer to the long-standing question of how the tumor suppressor ARF inhibits ribosome biogenesis, which does not involve p53 but is essential to prevent Ras-induced cell transformation.

6718 **ARID1A, a Factor That Promotes Formation of SWI/SNF-Mediated Chromatin Remodeling, Is a Tumor Suppressor in Gynecologic Cancers**

Bin Guan, Tian-Li Wang, and Ie-Ming Shih

Précis: A member of the SWI/SNF chromatin remodeling complex is shown to be a tumor suppressor in the development of several types of gynecological cancer, suggesting that aberrant chromatin remodeling activity has a central role in their pathogenesis.

6728 **An Iron Regulatory Gene Signature Predicts Outcome in Breast Cancer**

Lance D. Miller, Lan G. Coffman, Jeff W. Chou, Michael A. Black, Jonas Bergh, Ralph D'Agostino Jr, Suzy V. Torti, and Frank M. Torti

Précis: This study identifies a link between genes that govern iron metabolism and breast cancer prognosis, and suggests new tools that may ultimately help guide breast cancer prognosis.

6738 **Definition of a FoxA1 Cistrome That Is Crucial for G₁ to S-Phase Cell-Cycle Transit in Castration-Resistant Prostate Cancer**

Chunpeng Zhang, Liguang Wang, Dayong Wu, Hongyan Chen, Zhong Chen, Jennifer M. Thomas-Ahner, Debra L. Zynger, Jérôme Eeckhoutte, Jindan Yu, Jun Luo, Myles Brown, Steven K. Clinton, Kenneth P. Nephew, Tim H.-M. Huang, Wei Li, and Qianben Wang

Précis: A Forkhead transcription factor controlling global chromatin structure is a pivotal organizer of G₁-S cell cycle transit in castration-resistant prostate cancer.

PREVENTION AND EPIDEMIOLOGY

6749 **Urinary Levels of Cigarette Smoke Constituent Metabolites Are Prospectively Associated with Lung Cancer Development in Smokers**

Jian-Min Yuan, Yu-Tang Gao, Sharon E. Murphy, Steven G. Carmella, Renwei Wang, Yan Zhong, Kristin A. Moy, Andrew B. Davis, Li Tao, Menglan Chen, Shaomei Han, Heather H. Nelson, Mimi C. Yu, and Stephen S. Hecht

Précis: Metabolites of polycyclic aromatic hydrocarbon from cigarette smoke that appear in urine are independently associated with lung cancer risk, perhaps yielding a simple yet valuable monitoring tool in efforts to prevent lung cancer.

6758 **Shorter Telomeres Associate with a Reduced Risk of Melanoma Development**

Hongmei Nan, Mengmeng Du, Immaculata De Vivo, JoAnn E. Manson, Simin Liu, Anne McTiernan, J. David Curb, Lawrence S. Lessin, Matthew R. Bonner, Qun Guo, Abrar A. Qureshi, David J. Hunter, and Jiali Han

Précis: Findings challenge the traditional view that short telomeres are associated with increased risks of cancer, suggesting that telomeres have a unique role in the setting of cutaneous melanoma.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

6764 **Itraconazole Inhibits Angiogenesis and Tumor Growth in Non-Small Cell Lung Cancer**

Blake T. Aftab, Irina Dobromilskaya, Jun O. Liu, and Charles M. Rudin

Précis: The oral antifungal drug itraconazole demonstrates antiangiogenic efficacy in relevant tumor models of non-small cell lung cancer and is currently being tested in a phase II clinical trial of lung cancer patients.

6773 **A Kinome-Wide Screen Identifies the Insulin/IGF-I Receptor Pathway as a Mechanism of Escape from Hormone Dependence in Breast Cancer**

Emily M. Fox, Todd W. Miller, Justin M. Balko, Maria G. Kuba, Violeta Sánchez, R. Adam Smith, Shuying Liu, Ana María González-Angulo, Gordon B. Mills, Fei Ye, Yu Shyr, H. Charles Manning, Elizabeth Buck, and Carlos L. Arteaga

Précis: Clinical strategies to prevent ER+ breast cancers from escaping estrogen deprivation therapies are important to identify, because they could limit risks of progression to ER- cancers that are far more difficult to manage.

6785 **Expression and Immunotherapeutic Targeting of the SSX Family of Cancer-Testis Antigens in Prostate Cancer**

Heath A. Smith, Robert J. Cronk, Joshua M. Lang, and Douglas G. McNeel

Précis: Exclusive expression of a set of antigens expressed only in testis and metastatic prostate cancer may offer attractive targets for immunotherapy.

6796 **2-Deoxyglucose Induces Noxa-Dependent Apoptosis in Alveolar Rhabdomyosarcoma**

Silvia Ramírez-Peinado, Fermín Alcázar-Limones, Laura Lagares-Tena, Nadia El Mjiyad, Alfredo Caro-Maldonado, Oscar M. Tirado, and Cristina Muñoz-Pinedo

Précis: An aggressive pediatric muscle tumor was discovered to be highly sensitive to a glycolytic inhibitor similar to one used widely in the oncology clinic for PET imaging, suggesting it might be immediately repositioned as a therapeutic to treat what is often a fatal childhood cancer.

6807 **Verticillin A Overcomes Apoptosis Resistance in Human Colon Carcinoma through DNA Methylation-Dependent Upregulation of BNIP3**

Feiyan Liu, Qianqian Liu, Dafeng Yang, Wendy B. Bollag, Keith Robertson, Ping Wu, and Kebin Liu

Précis: To combat drug resistance, the primary cause of deaths from cancer, one top goal of laboratory research is to identify adjuvants that can safely and effectively cooperate with existing treatments to widen their therapeutic window of action.

6817 **Inhibition of Neurotensin Receptor 1 Selectively Sensitizes Prostate Cancer to Ionizing Radiation**

Nicholas C.K. Valerie, Eli V. Casarez, John O. DaSilva, Marya E. Dunlap-Brown, Sarah J. Parsons, George P. Amorino, and Jaroslaw Dziegielewski

Précis: A receptor that is absent from normal prostate cells, but switched on in prostate cancers, offers a therapeutic target for radiosensitizing this malignancy.

6827 **Cell-Cycle Regulator Cks1 Promotes Hepatocellular Carcinoma by Supporting NF-κB-Dependent Expression of Interleukin-8**

Eun-Kyoung Lee, Dae-Ghon Kim, Jang-Seong Kim, and Yeup Yoon

Précis: Findings link an important cell cycle regulator to NF-κB control of a central regulator of the inflammatory tumor microenvironment, illustrating how the cell division processes of cancer cells are perhaps invariably linked to their coordination of local immune support.

6836 **A NOTCH3-Mediated Squamous Cell Differentiation Program Limits Expansion of EMT-Competent Cells That Express the ZEB Transcription Factors**

Shinya Ohashi, Mitsuteru Natsuzaka, Seiji Naganuma, Shingo Kagawa, Sotai Kimura, Hiroshi Itoh, Ross A. Kalman, Momo Nakagawa, Douglas S. Darling, Devraj Basu, Phyllis A. Gimotty, Andres J. Klein-Szanto, J. Alan Diehl, Meenhard Herlyn, and Hiroshi Nakagawa

Précis: Novel insights into the progression of a class of esophageal cancers rising rapidly in incidence are provided by this mechanistic study of how Notch3 receptor signaling acts to prevent expansion of aggressive clones that can emerge during tumorigenesis.

6848 **Generation of a Mouse Model of Von Hippel-Lindau Kidney Disease Leading to Renal Cancers by Expression of a Constitutively Active Mutant of HIF1α**

Leiping Fu, Gang Wang, Maria M. Shevchuk, David M. Nanus, and Lorraine J. Gudas

Précis: This study describes a new transgenic mouse model for von Hippel-Lindau (VHL) kidney disease that mimics the genetic and molecular events leading to human renal cell carcinoma.

6857 **Breast Cancer Subtype-Specific Interactions with the Microenvironment Dictate Mechanisms of Invasion**

Tuyen T. Dang, Amanda M. Prechtel, and Gray W. Pearson

Précis: Real-time imaging of tumor-fibroblast interactions in breast cancer suggests how interactions with the microenvironment control malignant progression, and also how basal and luminal subtypes of breast cancer do not progress in the same way.

6867

TNF- α Promotes c-REL/ Δ Np63 α Interaction and TAp73 Dissociation from Key Genes That Mediate Growth Arrest and Apoptosis in Head and Neck Cancer

Hai Lu, Xiping Yang, Praveen Duggal, Clint T. Allen, Bin Yan, Jonah Cohen, Liesl Nottingham, Rose-Anne Romano, Satrajit Sinha, Kathryn E. King, Wendy C. Weinberg, Zhong Chen, and Carter Van Waes

Précis: Inflammatory signals in the tumor microenvironment can attenuate tumor suppressor functions in cancer cells, as illustrated by this study of how TNF- β and the NF- κ B oncoprotein c-REL repress the antiproliferative and proapoptotic activities of Δ Np63-bound p73 in cancer cells harboring mutant p53.

6878

FOXO3a-Dependent Mechanism of E1A-Induced Chemosensitization

Jen-Liang Su, Xiaoyun Cheng, Hirohito Yamaguchi, Yi-Wen Chang, Chao-Feng Hou, Dung-Fang Lee, How-Wen Ko, Kuo-Tai Hua, Ying-Nai Wang, Michael Hsiao, PoShen B. Chen, Jung-Mao Hsu, Robert C. Bast, Jr, Gabriel N. Hortobagyi, and Mien-Chie Hung

Précis: By providing a leap forward in understanding how the adenovirus oncoprotein E1A sensitizes cancer cells to paclitaxel, this study provides a strong mechanistic rationale to use E1A gene therapy which has been tested clinically as an adjuvant to chemosensitize cancers to this widely used antimitotic drug.

6888

PGC1 α Promotes Tumor Growth by Inducing Gene Expression Programs Supporting Lipogenesis

Kavita Bhalla, Bor Jang Hwang, Ruby E. Dewi, Lihui Ou, William Twaddel, Hong-bin Fang, Scott B. Vafai, Francesca Vazquez, Pere Puigserver, Laszlo Boros, and Geoffrey D. Girnun

Précis: Results show how a central regulator of energy metabolism controls multiple metabolic pathways to drive carcinogenesis and cancer growth.

6899

Binding of the JmjC Demethylase JARID1B to LSD1/NuRD Suppresses Angiogenesis and Metastasis in Breast Cancer Cells by Repressing Chemokine CCL14

Qian Li, Lei Shi, Bin Gui, Wenhua Yu, Jiamu Wang, Di Zhang, Xiao Han, Zhi Yao, and Yongfeng Shang

Précis: Findings define a novel pharmaceutically tractable target that is part of an important transcriptional repression complex broadly implicated in malignant progression.

OBITUARY

6909

On the Passing of Gerald C. Mueller, MD, PhD (1920–2010)

CORRECTIONS

6911

Correction: A Requirement of STAT3 DNA-Binding Precludes Th-1 Immunostimulatory Gene Expression by NF- κ B in Tumors

6912

Correction: Online Publication Date for *Cancer Research* September 1, 2011, Article

ABOUT THE COVER

Macrophages play a key role in tumor growth, invasion, and metastasis. Phipps and colleagues identified the mechanism that controls the migration of macrophages to the tumor site. They showed that the generation of plasmin at the cell surface of the macrophage is regulated by the plasminogen receptor S100A10, and that S100A10-regulated plasmin generation is necessary for both the movement of the macrophages to the tumor site and tumor growth and vascularization. The photomicrograph shows that the vascular density, monitored by CD31 immunofluorescence (green), of Lewis lung carcinoma tumors grown in S100A10-null mice can be restored by the adoptive transfer of wild-type macrophages. For details, see the article by Phipps and colleagues on page 6676 of this issue.

