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Cancer Research

October 1, 2011 • Volume 71 • Number 19

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Carina Signori, Karam El-Bayoumy, Jose Russo, Henry J. Thompson, John P. Richie, Terryl J. Hartman, and Andrea Manni

- 6116 | **Effects of Photoacoustic Imaging and Photothermal Ablation Therapy Mediated by Targeted Hollow Gold Nanospheres in an Orthotopic Mouse Xenograft Model of Glioma**
Wei Lu, Marites P. Melancon, Chiyi Xiong, Qian Huang, Andrew Elliott, Shaoli Song, Rui Zhang, Leo G. Flores II, Juri G. Gelovani, Lihong V. Wang, Geng Ku, R. Jason Stafford, and Chun Li

Précis: Multifunctional targeted hollow gold nanospheres serve as a new cancer theranostic platform for both photoacoustic imaging and photothermal ablation therapy.

MEETING REPORTS

- 6097 | **IDIBELL Cancer Conference on Metastasis and Angiogenesis**
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PRIORITY REPORTS

- 6106 | **Downregulation of RBMS3 Is Associated with Poor Prognosis in Esophageal Squamous Cell Carcinoma**
Yan Li, Leilei Chen, Chang-jun Nie, Ting-ting Zeng, Haibo Liu, Xueying Mao, Yanru Qin, Ying-Hui Zhu, Li Fu, and Xin-Yuan Guan
- Précis:* Findings identify a novel tumor suppressor gene in esophageal squamous cell carcinoma that functions via downregulation of c-Myc.

MICROENVIRONMENT AND IMMUNOLOGY

- 6122 | **Resuscitating Cancer Immunosurveillance: Selective Stimulation of DLL1-Notch Signaling in T cells Rescues T-cell Function and Inhibits Tumor Growth**
Yuhui Huang, Luping Lin, Anil Shanker, Anshu Malhotra, Li Yang, Mikhail M. Dikov, and David P. Carbone

Précis: Definition of a novel pathway of immune escape mediated by attenuation of Notch signaling in T cells suggests a generalized strategy to activate T cell-mediated destruction of tumor cells in clinical trials.

- 6132 | **FLT3 Ligand Enhances the Cancer Therapeutic Potency of Naked RNA Vaccines**
Sebastian Kreiter, Mustafa Diken, Abderraouf Selmi, Jan Diekmann, Sebastian Attig, Yves Hüsemann, Michael Koslowski, Christoph Huber, Özlem Türeci, and Ugur Sahin

Précis: This study reports an adjuvant strategy to strengthen the antitumor effects achieved by lymph node injection with naked RNA encoding tumor antigens, optimizing a safe and simple vaccination strategy for cancer immunotherapy.

- 6143 **Early Detection of Tumor Cells by Innate Immune Cells Leads to T_{reg} Recruitment through CCL22 Production by Tumor Cells**
Julien Faget, Cathy Biota, Thomas Bachelot, Michael Gobert, Isabelle Treilleux, Nadège Goutagny, Isabelle Durand, Sophie Léon-Goddard, Jean Yves Blay, Christophe Caux, and Christine Ménétrier-Caux

Précis: This important study addresses the key question of how early tumor cells evolve the ability to escape roving innate immune cells by recruiting tumor-promoting T regulatory cells (Tregs), thought to be central drivers of cancer progression.

- 6174 **Cyclin D1 and Cdk4 Mediate Development of Neurologically Destructive Oligodendroglioma**
Daniel Ciznadija, Yuhui Liu, Stephanie M. Pyonteck, Eric C. Holland, and Andrew Koff

Précis: This seminal in vivo study establishes that the Cyclin D1-Cdk4 complex—the central regulator of cell proliferation in human cancer cells—is not only important in tumor cells but also in stromal cells of the surrounding microenvironment that are critical for tumor outgrowth.

- 6184 **Wnt5a Suppresses Epithelial Ovarian Cancer by Promoting Cellular Senescence**
Benjamin G. Bitler, Jasmine P. Nicodemus, Hua Li, Qi Cai, Hong Wu, Xiang Hua, Tianyu Li, Michael J. Birrer, Andrew K. Godwin, Paul Cairns, and Rugang Zhang

Précis: Findings define a tumor suppressor function that when downregulated in ovarian cancer patients confers a poor prognosis for outcomes.

MOLECULAR AND CELLULAR PATHOBIOLOGY

- 6153 **Proto-oncogene PBF/PTTG1IP Regulates Thyroid Cell Growth and Represses Radioiodide Treatment**
Martin L. Read, Greg D. Lewy, Jim C.W. Fong, Neil Sharma, Robert I. Seed, Vicki E. Smith, Erica Gentilin, Adrian Warfield, Margaret C. Eggo, Jeffrey A. Knauf, Wendy E. Leadbeater, John C. Watkinson, Jayne A. Franklyn, Kristien Boelaert, and Christopher J. McCabe

Précis: A little-characterized proto-oncogene in thyroid hyperplasia and neoplasia functions in blocking the chief route of radioiodine uptake, which is vital for clinical treatment of thyroid cancer.

- 6165 **miR-375 Is Activated by ASH1 and Inhibits YAP1 in a Lineage-Dependent Manner in Lung Cancer**
Eri Nishikawa, Hirotaka Osada, Yasumasa Okazaki, Chinatsu Arima, Shuta Tomida, Yoshio Tatematsu, Ayumu Taguchi, Yukako Shimada, Kiyoshi Yanagisawa, Yasushi Yatabe, Shinya Toyokuni, Yoshitaka Sekido, and Takashi Takahashi

Précis: Findings provide insight into the molecular determinants of small cell lung cancers with neuroendocrine features, which tend to be aggressive and difficult to treat.

- 6195 **Genome-wide Methylation Analysis Identifies Genes Specific to Breast Cancer Hormone Receptor Status and Risk of Recurrence**
Mary Jo Fackler, Christopher B. Umbricht, Danielle Williams, Pedram Argani, Leigh-Ann Cruz, Vanessa F. Merino, Wei Wen Teo, Zhe Zhang, Peng Huang, Kala Visvanathan, Jeffrey Marks, Stephen Ethier, Joe W. Gray, Antonio C. Wolff, Leslie M. Cope, and Saraswati Sukumar

Précis: Methylome analysis of primary breast cancers led to the identification of 40 markers that segregated ER+ from ER- breast cancers and 32 markers that predicted risk of recurrence, and sets the stage for further discovery in samples from large clinical trials.

- 6208 **MicroRNA-708 Induces Apoptosis and Suppresses Tumorigenicity in Renal Cancer Cells**
Sharanjot Saini, Soichiro Yamamura, Shahana Majid, Varahram Shahryari, Hiroshi Hirata, Yuichiro Tanaka, and Rajvir Dahiya

Précis: This study reveals a major suppressor role for a little-studied microRNA in the pathogenesis of a highly aggressive kidney malignancy, mediated in large part by its ability to inhibit expression of the antiapoptotic protein survivin, which is widely overexpressed in human cancers.

6220

A Mutation Threshold Distinguishes the Antitumorigenic Effects of the Mitochondrial Gene *MTND1*, an *Oncojanus* Function

Giuseppe Gasparre, Ivana Kurelac, Mariantonietta Capristo, Luisa Iommarini, Anna Ghelli, Claudio Ceccarelli, Giordano Nicoletti, Patrizia Nanni, Carla De Giovanni, Katia Scotlandi, Christine M. Betts, Valerio Carelli, Pier Luigi Lollini, Giovanni Romeo, Michela Rugolo, and Anna Maria Porcelli

Précis: This study reinterprets the role of mitochondrial DNA mutations in cancer progression and adds a novel functional definition for metabolic genes with a threshold-dependent lethality effect.

6230

MicroRNA-32 Upregulation by 1,25-Dihydroxyvitamin D₃ in Human Myeloid Leukemia Cells Leads to Bim Targeting and Inhibition of AraC-Induced Apoptosis

Elzbieta Gocek, Xuening Wang, Xiuping Liu, Chang-Gong Liu, and George P. Studzinski

Précis: Treatment of acute myeloid leukemias that remain poorly managed in the clinic may benefit from agents that can block the expression of a microRNA that limits expression of the pro-apoptotic protein Bim.

PREVENTION AND EPIDEMIOLOGY

6240

Common Breast Cancer Susceptibility Loci Are Associated with Triple-Negative Breast Cancer

Kristen N. Stevens, Celine M. Vachon, Adam M. Lee, Susan Slager, Timothy Lesnick, Curtis Olswold, Peter A. Fasching, Penelope Miron, Diana Eccles, Jane E. Carpenter, Andrew K. Godwin, Christine Ambrosone, Robert Winqvist, Hiltrud Brauch on behalf of the GENICA consortium, Marjanka K. Schmidt, Angela Cox, Simon S. Cross, Elinor Sawyer, Arndt Hartmann, Matthias W. Beckmann, Rüdiger Schulz-Wendtland, Arif B. Ekici, William J. Tapper, Susan M. Gerty, Lorraine Durcan, Nikki Graham, Rebecca Hein, Stephan Nickels, Dieter Flesch-Janys, Judith Heinz, Hans-Peter Sinn, Irene Konstantopoulou, Florentia Fostira, Dimitrios Pectasides, Athanasios M. Dimopoulos, George Fountzilas, Christine L. Clarke, Rosemary Balleine, Janet E. Olson, Zachary Fredericksen, Robert B. Diasio, Harsh Pathak, Eric Ross, JoEllen Weaver, Thomas Rüdiger, Asta Försti, Thomas Dünnebier, Foluso Ademuyiwa, Swati Kulkarni, Katri Pylkäs, Arja Jukkola-Vuorinen, Yon-Dschun Ko, Erik Van Limbergen, Hilde Janssen, Julian Peto, Olivia Fletcher, Graham G. Giles, Laura Baglietto,

Senno Verhoef, Ian Tomlinson, Veli-Matti Kosma, Jonathan Beesley, Dario Greco, Carl Blomqvist, Astrid Irwanto, Jianjun Liu, Fiona M. Blows, Sarah-Jane Dawson, Sara Margolin, Arto Mannermaa, Nicholas G. Martin, Grant W. Montgomery, Diether Lambrechts, Isabel dos Santos Silva, Gianluca Severi, Ute Hamann, Paul Pharoah, Douglas F. Easton, Jenny Chang-Claude, Drakoulis Yannoukakos, Heli Nevanlinna, Xianshu Wang, and Fergus J. Couch

Précis: This first report from a large consortium identifies variants in the *ESR1*, *MERIT40*, *RAD51L1*, and *TOX3* genes that were found to be highly significantly associated with risk of triple negative breast cancer.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

6250

Androgen-Independent Molecular Imaging Vectors to Detect Castration-Resistant and Metastatic Prostate Cancer

Ziyue Karen Jiang, Makoto Sato, Liu H. Wei, Chinghai Kao, and Lily Wu

Précis: A prostate cancer-specific but androgen-independent imaging reporter system is shown to be useful for detecting advanced castration-resistant prostate cancer, including disseminated bony metastases.

6261

EGF Receptor Inhibition Radiosensitizes NSCLC Cells by Inducing Senescence in Cells Sustaining DNA Double-Strand Breaks

Meng Wang, Fabian Morsbach, David Sander, Liliana Gheorghiu, Akash Nanda, Cyril Benes, Malte Kriegs, Mechthild Krause, Ekkehard Dikomey, Michael Baumann, Jochen Dahm-Daphi, Jeffrey Settleman, and Henning Willers

Précis: This study offers a mechanistic rationale to reposition EGF inhibitors used widely in the clinic as radiosensitizers in lung cancer.

6270

Celecoxib Promotes c-FLIP Degradation through Akt-Independent Inhibition of GSK3

Shuzhen Chen, Wei Cao, Ping Yue, Chunhai Hao, Fadlo R. Khuri, and Shi-Yong Sun

Précis: Mechanistic findings reveal insights into how celecoxib may promote cancer cell death by promoting turnover of c-FLIP, a chief regulator of the death receptor pathway of apoptosis.

TUMOR AND STEM CELL BIOLOGY

6282

Transplantation of β -Endorphin Neurons into the Hypothalamus Promotes Immune Function and Restricts the Growth and Metastasis of Mammary Carcinoma

Dipak K. Sarkar, Changqing Zhang,
Sengottuvelan Murugan, Madhavi Dokur,

Nadka I. Boyadjieva, Maria Ortigüela,
Kenneth R. Reuhl, and Sepide Mojtehdzadeh

Precis: Stress blunts the effects of a mood-altering molecule that appears to affect the innate immune response to tumors, suggesting a role in tumorigenesis for an inflammatory reflex that integrates neuronal and immune signaling in the body.

ABOUT THE COVER

β -endorphin (bEP) neuron activation prevents the growth and metastasis of mammary tumor cells by altering autonomic nervous system activities that enhance innate immune functions. Sarkar and colleagues identified the mechanism by which bEP cell transplantation into the brain prevents mammary carcinogenesis by showing that the transplants' antimetastatic effect, along with stimulation of cytotoxic function of immune cells and production of anti-inflammatory cytokines, is reversed by the treatment with an opiate antagonist, naloxone (NAL), to block bEP, the β -receptor agonist metaproterenol (MET) to activate sympathetic neurotransmission, or the nicotine acetylcholine receptor antagonist methyllycaconitine (MLA) to prevent parasympathetic neurotransmission. For details, see the article by Sarkar and colleagues on page 6282 of this issue.

