

BREAKING ADVANCES

- 5909** Highlights from Recent Cancer Literature

CANCER RESEARCH 75TH ANNIVERSARY COMMENTARY

- 5911** A Decade of Nilotinib and Dasatinib: From *In Vitro* Studies to First-Line Tyrosine Kinase Inhibitors
Thomas O'Hare

REVIEWS

- 5914** Finally, An Apoptosis-Targeting Therapeutic for Cancer
Carlo M. Croce and John C. Reed
- 5921** Concepts in Cancer Modeling: A Brief History
Renee M. Thomas, Terry Van Dyke, Glenn Merlino, and Chi-Ping Day

PRIORITY REPORT

- 5926** Anticancer Effects of Targeting Hsp70 in Tumor Stromal Cells
Vladimir L. Gabai, Julia A. Yaglom, Yongmei Wang, Le Meng, Hao Shao, Geunwon Kim, Teresa Colvin, Jason Gestwicki, and Michael Y. Sherman
- Précis:* This important study shows that Hsp70 inhibitors target tumor-associated macrophages, which enable the progression of many cancers, offering a rationale for broad application of these candidate therapeutic agents.

CLINICAL STUDIES

- 5933** Predicting Responses to Neoadjuvant Chemotherapy in Breast Cancer: ACRIN 6691 Trial of Diffuse Optical Spectroscopic Imaging
Bruce J. Tromberg, Zheng Zhang, Anaïs Leproux, Thomas D. O'Sullivan, Albert E. Cerussi, Philip M. Carpenter, Rita S. Mehta, Darren Roblyer, Wei Yang, Keith D. Paulsen, Brian W. Pogue, Shudong Jiang, Peter A. Kaufman, Arjun G. Yodh, So Hyun Chung, Mitchell Schnall, Bradley S. Snyder, Nola Hylton, David A. Boas, Stefan A. Carp, Steven J. Isakoff, and David Mankoff, on behalf of the ACRIN 6691 investigators

Précis: Endpoints evaluated in a multicenter study of an experimental optical imaging technology could predict pathologic complete responses in breast cancer patients who received chemotherapy before other interventions, a treatment design that appears to be more efficacious in many patients than older designs where chemotherapy is only used afterward.

- 5945** Water Concentration Analysis by Raman Spectroscopy to Determine the Location of the Tumor Border in Oral Cancer Surgery
Elisa M. Barroso, Roeland W.H. Smits, Cornelia G.F. van Lanschot, Peter J. Caspers, Ivo ten Hove, Hetty Mast, Aniel Sewnaik, José A. Hardillo, Cees A. Meeuwis, Rob Verdijk, Vincent Noordhoek Hegt, Robert J. Baatenburg de Jong, Eppo B. Wolvius, Tom C. Bakker Schut, Senada Koljenović, and Gerwin J. Puppels

Précis: These findings highlight the potential of Raman spectroscopy to make rapid and objective intraoperative assessments of tumor resection margins in the operating room.

INTEGRATED SYSTEMS AND TECHNOLOGIES

- 5954** Improving the Performance of Somatic Mutation Identification by Recovering Circulating Tumor DNA Mutations
Yu Fu, Cécile Jovelet, Thomas Filleron, Marion Pedrero, Nelly Motté, Yannick Boursin, Yufei Luo, Christophe Massard, Mario Campone, Christelle Levy, Véronique Diéras, Thomas Bachelot, Julie Garrabey, Jean-Charles Soria, Ludovic Lacroix, Fabrice André, and Celine Lefebvre

Précis: This study describes the first computational method to systematically identify circulating tumor DNA mutations in the blood of cancer patients through the comparison of whole-exome sequencing data from paired tumor and blood samples from a patient.

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5962 Bronchial Artery Angiogenesis Drives Lung Tumor Growth



Lindsey Eldridge, Aigul Moldobaeva, Qiong Zhong, John Jenkins, Michael Snyder, Robert H. Brown, Wayne Mitzner, and Elizabeth M. Wagner

Précis: These findings present a new model, suggesting that targeting the bronchial endothelium may permit the development of new approaches to treat lung cancer.

MICROENVIRONMENT AND IMMUNOLOGY

5970 Immune-Stimulatory Effects of Rapamycin Are Mediated by Stimulation of Antitumor $\gamma\delta$ T Cells

Vinh Dao, Yang Liu, Srilakshmi Pandeswara, Robert S. Svatek, Jonathan A. Gelfond, Aijie Liu, Vincent Hurez, and Tyler J. Curiel

Précis: This seminal report challenges the paradigm that the anticancer effects of mTOR inhibitors are due primarily to a direct effect on tumor cells.

5983 Evidence Implicating Immunological Host Effects in the Efficacy of Metronomic Low-Dose Chemotherapy

Yuval Shaked, Elizabeth Pham, Santosh Hariharan, Ksenia Magidey, Ofrat Beyar-Katz, Ping Xu, Shan Man, Florence T.H. Wu, Valeria Miller, David Andrews, and Robert S. Kerbel

Précis: High-throughput systems analyses used in this study identify candidate biomarkers that may predict clinical outcomes to metronomic chemotherapy.

5994 Abscopal Effects of Radiotherapy Are Enhanced by Combined Immunostimulatory mAbs and Are Dependent on CD8 T Cells and Crosspriming

María E. Rodriguez-Ruiz, Inmaculada Rodriguez, Saray Garasa, Benigno Barbes, Jose Luis Solorzano, Jose Luis Perez-Gracia, Sara Labiano, Miguel F. Sanmamed, Arantza Azpilikueta, Elixabet Bolaños, Alfonso R. Sanchez-Paulete, M. Angela Aznar, Ana Rouzaut, Kurt A. Schalper, Maria Jure-Kunkel, and Ignacio Melero

Précis: Therapy with immunomodulatory monoclonal antibodies can leverage the effects of radiotherapy outside the irradiation field—termed abscopal effects—with immediate implications for clinical translation.

6006 Efficacy of Adoptive T-cell Therapy Is Improved by Treatment with the Antioxidant N-Acetyl Cysteine, Which Limits Activation-Induced T-cell Death

Matthew J. Scheffel, Gina Scurti, Patricia Simms, Elizabeth Garrett-Mayer, Shikhar Mehrotra, Michael I. Nishimura, and Christina Voelkel-Johnson

Précis: These results offer preclinical proof of concept for a method to improve current protocols used to expand therapeutic T cells before they are infused into patients, offering an immediate impact on the quality and therapeutic efficacy of adoptive T-cell therapeutic products.

6017 Tumor Eradication by Cisplatin Is Sustained by CD80/86-Mediated Costimulation of CD8⁺ T Cells

Elham Beyranvand Nejad, Tetje C. van der Sluis, Suzanne van Duikeren, Hideo Yagita, George M. Janssen, Peter A. van Veelen, Cornelis J.M. Melief, Sjoerd H. van der Burg, and Ramon Arens

Précis: Many chemotherapeutic drugs that kill cancer cells by damaging DNA also exert ‘immunogenic’ properties that stimulate tumor immunity, which in the case of the widely used drug cisplatin appear to be mediated by induction of costimulatory signals for antitumor CD8⁺ T cells.

6030 Chemotherapy-Induced IL34 Enhances Immunosuppression by Tumor-Associated Macrophages and Mediates Survival of Chemoresistant Lung Cancer Cells

Muhammad Baghdadi, Haruka Wada, Sayaka Nakanishi, Hirotake Abe, Nanumi Han, Wira Eka Putra, Daisuke Endo, Hidemichi Watari, Noriaki Sakuragi, Yasuhiro Hida, Kichizo Kaga, Yohei Miyagi, Tomoyuki Yokose, Atsushi Takano, Yataro Daigo, and Ken-ichiro Seino

Précis: This study identifies a readily tractable target to relieve the immunosuppressive and chemoresistance effects of tumor-associated macrophages in the cancer microenvironment.

MOLECULAR AND CELLULAR PATHOBIOLOGY

6043 SMYD3-Mediated H2A.Z.1 Methylation Promotes Cell Cycle and Cancer Proliferation

Cheng-Hui Tsai, Yun-Ju Chen, Chia-Jung Yu, Shiou-Ru Tzeng, I-Chen Wu, Wen-Hung Kuo, Ming-Chieh Lin, Nei-Li Chan, Kou-Juey Wu, and Shu-Chun Teng

Précis: These results define an oncogenic function for a protein methyltransferase that can accelerate proliferation in breast cancer cells, with possible therapeutic implications, given the specificity of its expression in certain types of breast cancer.

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- 6054** INT6/EIF3E Controls the RNF8-Dependent Ubiquitylation Pathway and Facilitates DNA Double-Strand Break Repair in Human Cells
Christelle Morris, Nozomi Tomimatsu, Sandeep Burma, and Pierre Jalinot

Précis: This study illuminates an anticancer factor that helps prevent breast cancer by establishing how it functions in DNA repair, with potential clinical implications for cancer therapy.

PREVENTION AND EPIDEMIOLOGY

- 6066** Impact of Serum Antibodies to HPV Serotypes 6, 11, 16, and 18 to Risks of Subsequent Genital HPV Infections in Men: The HIM Study
Shitaldas J. Pamnani, Staci L. Sudenga, Raphael Viscidi, Dana E. Rollison, B. Nelson Torres, Donna J. Ingles, Martha Abrahamsen, Luisa L. Villa, Eduardo Lazcano-Ponce, Jorge Salmeron, Manuel Quiterio, Yangxin Huang, Amy Borenstein, and Anna R. Giuliano

Précis: These findings suggest that men remain mainly susceptible to HPV infection after earlier natural infections have occurred, such that vaccination and other preventive methods may be required to control genital HPV infections and their associated diseases in men and women.

- 6076** Body Mass Index, Waist Circumference, Diabetes, and Risk of Liver Cancer for U.S. Adults
Peter T. Campbell, Christina C. Newton, Neal D. Freedman, Jill Koshiol, Michael C. Alavanja, Laura E. Beane Freeman, Julie E. Buring, Andrew T. Chan, Dawn Q. Chong, Mridul Datta, Mia M. Gaudet, J. Michael Gaziano, Edward L. Giovannucci, Barry I. Graubard, Albert R. Hollenbeck, Lindsey King, I.-Min Lee, Martha S. Linet, Julie R. Palmer, Jessica L. Petrick, Jenny N. Poynter, Mark P. Purdue, Kim Robien, Lynn Rosenberg, Vikrant V. Sahasrabudde, Catherine Schairer, Howard D. Sesso, Alice J. Sigurdson, Victoria L. Stevens, Jean Wactawski-Wende, Anne Zeleniuch-Jacquotte, Andrew G. Renehan, and Katherine A. McGlynn

Précis: High body mass index, high waist circumference, and diabetes are major independent risk factors for liver cancer in the U.S. and may relate to the relatively rapid increase in the incidence of liver cancer among U.S. adults in recent decades.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

- 6084** The PARP Inhibitor AZD2461 Provides Insights into the Role of PARP3 Inhibition for Both Synthetic Lethality and Tolerability with Chemotherapy in Preclinical Models



Lenka Oplustil O'Connor, Stuart L. Rulten, Aaron N. Cranston, Rajesh Odedra, Henry Brown, Janneke E. Jaspers, Louise Jones, Charlotte Knights, Bastiaan Evers, Atilla Ting, Robert H. Bradbury, Marina Pajic, Sven Rottenberg, Jos Jonkers, David Rudge, Niall M.B. Martin, Keith W. Caldecott, Alan Lau, and Mark J. O'Connor

Précis: Characterization of a next-generation PARP inhibitor demonstrates utility in BRCA-mutant mouse models of olaparib resistance, highlighting a dependence on the particular species being tested as well as the extent of PARP3 inhibitory activity in predicting tolerability in combination with chemotherapy.

- 6095** Deep Sequencing Reveals a Novel miR-22 Regulatory Network with Therapeutic Potential in Rhabdomyosarcoma

Francesca Bersani, Marcello Francesco Lingua, Deborah Morena, Valentina Foglizzo, Silvia Miretti, Letizia Lanzetti, Giovanna Carrà, Alessandro Morotti, Ugo Ala, Paolo Provero, Roberto Chiarle, Samuel Singer, Marc Ladanyi, Thomas Tuschl, Carola Ponzetto, and Riccardo Taulli

Précis: These results identify a novel miR-22 regulatory network that opposes the invasive growth of the pediatric muscle tumor rhabdomyosarcoma by intercepting an ERBB3-MEK pathway.

TUMOR AND STEM CELL BIOLOGY

- 6107** WWOX and p53 Dysregulation Synergize to Drive the Development of Osteosarcoma

Sara Del Mare, Hussam Husanie, Ortal Iancu, Mohammad Abu-Odeh, Konstantinos Evangelou, Francesca Lovat, Stefano Volinia, Jonathan Gordon, Gail Amir, Janet Stein, Gary S. Stein, Carlo M. Croce, Vassilis Gorgoulis, Jane B. Lian, and Rami I. Aqeilan

Précis: Combined genetic inactivation of the tumor suppressors WWOX and p53 in bone osteoblasts in mice is sufficient to induce the development of aggressive osteosarcomas, offering an improved model of human disease useful for studies of molecular pathogenesis and therapy.

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6118 CRISPR/Cas9-Mediated *Trp53* and *Brca2* Knockout to Generate Improved Murine Models of Ovarian High-Grade Serous Carcinoma



Josephine Walton, Julianna Blagih, Darren Ennis, Elaine Leung, Suzanne Dowson, Malcolm Farquharson, Laura A. Tookman, Clare Orange, Dimitris Athineos, Susan Mason, David Stevenson, Karen Blyth, Douglas Strathdee, Frances R. Balkwill, Karen Vousden, Michelle Lockley, and Iain A. McNeish

Précis: This study introduces a simple useful model of transplantable ovarian carcinoma that recreates the critical mutations seen in human ovarian high-grade serous carcinoma needed to investigate relationships between tumor genotype, immune microenvironment, and therapeutic drug responses.

CORRECTIONS

6130 Correction: TALEN-Mediated Inactivation of PD-1 in Tumor-Reactive Lymphocytes Promotes Intratumoral T-cell Persistence and Rejection of Established Tumors

6131 Correction: Endothelial ALK1 Is a Therapeutic Target to Block Metastatic Dissemination of Breast Cancer

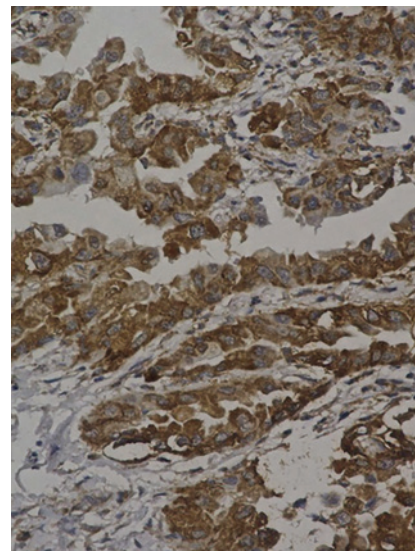
6133 Correction: Diverse Targets of β -Catenin during the Epithelial–Mesenchymal Transition Define Cancer Stem Cells and Predict Disease Relapse

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ABOUT THE COVER

IL34 is expressed in primary lung adenocarcinoma tissues and correlates with poor prognosis in cancer patients. IL34, a cytokine that acts as a second ligand for CSF1R, was found to be induced and controlled by chronic activation of NF- κ B in chemoresistant lung cancer cells. *In vitro* and *in vivo* experiments unveiled a dual role for IL34 in cancer chemoresistance. IL34 was found to enhance local immunosuppression by tumor-associated macrophages and also provides cancer cells with a critical survival signal to overcome chemotherapeutic conditions. For details, see article by Baghdadi and colleagues on page 6030.



Cancer Research

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

76 (20)

Cancer Res 2016;76:5909-6133.

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