


## BREAKING ADVANCES

- 3381** Highlights from Recent Cancer Literature

## OBITUARY

- 3383** Enrico Mihich, MD: In Memoriam (1928–2016)  
Margaret Foti and Youcef M. Rustum

## MEETING REPORT


- 3386** Obstacles, Opportunities and Priorities for Advancing Metastatic Breast Cancer Research  
 Margaret Flowers, Stephanie Birkey Reffey, Shirley A. Mertz, and Marc Hurlbert, for the Metastatic Breast Cancer Alliance

## MOLECULAR AND CELLULAR PATHOBIOLOGY

- 3391** Cyclin D1 Restrains Oncogene-Induced Autophagy by Regulating the AMPK–LKB1 Signaling Axis  
Mathew C. Casimiro, Gabriele Di Sante, Agnese Di Rocco, Emanuele Loro, Claudia Pupo, Timothy G. Pestell, Sara Bisetto, Marco A. Velasco-Velázquez, Xuanmao Jiao, Zhiping Li, Christine M. Kusminski, Erin L. Seifert, Chenguang Wang, Daniel Ly, Bin Zheng, Che-Hung Shen, Philipp E. Scherer, and Richard G. Pestell  
*Précis:* These findings suggest how AMPK activation by cyclin D1 may couple cell proliferation to energy homeostasis.

- 3406** VHL Inactivation in Precancerous Kidney Cells Induces an Inflammatory Response via ER Stress–Activated IRE1 $\alpha$  Signaling  
Chan-Yen Kuo, Chih-Hung Lin, and Tien Hsu  
*Précis:* A tumor suppressor gene mutation in normal epithelial cells can induce inflammatory response via ER stress signaling, thus providing a potential early cancer prevention strategy via modulation of metabolic stress.

## TUMOR AND STEM CELL BIOLOGY

- 3417** Novel Androgen Receptor Coregulator GRHL2 Exerts Both Oncogenic and Antimetastatic Functions in Prostate Cancer  
Steve Paltoglou, Rajdeep Das, Scott L. Townley, Theresa E. Hickey, Gerard A. Tarulli, Isabel Coutinho, Rayzel Fernandes, Adrienne R. Hanson, Iza Denis, Jason S. Carroll, Scott M. Dehm, Ganesh V. Raj, Stephen R. Plymate, Wayne D. Tilley, and Luke A. Selth  
*Précis:* These results show how a grainyhead-like transcription factor enhances androgen receptor expression and activity, driving proliferation of prostate cancer cells, but it also acts differentially to limit their metastatic capacity.
- 3431** Liver Metastasis Is Facilitated by the Adherence of Circulating Tumor Cells to Vascular Fibronectin Deposits  
 Jorge Barbazán, Lorena Alonso-Alconada, Nadia Elkhatib, Sara Geraldo, Vasily Gurchenkov, Alexandros Glentis, Guillaume van Niel, Roberta Palmulli, Beatriz Fernández, Patricia Viaño, Tomas García-Caballero, Rafael López-López, Miguel Abal, and Danijela Matic Vignjevic  
*Précis:* Fibronectin accumulations at the luminal side of liver blood vessels act as an anchor for cancer cells, revealing an important new mechanism of extravasation with potential therapeutic implications to retard metastatic risk.
- 3442** Distinct Roles of HES1 in Normal Stem Cells and Tumor Stem-like Cells of the Intestine  
Norihiro Goto, Taro Ueo, Akihisa Fukuda, Kenji Kawada, Yoshiharu Sakai, Hiroyuki Miyoshi, Makoto Mark Taketo, Tsutomu Chiba, and Hiroshi Seno  
*Précis:* These results show how a stem cell transcription factor plays a different role in cancer stem-like cells, where its disruption leads to tumor regression without perturbing normal stem cell homeostasis, thereby validating it as a cancer therapeutic target.
- 3455** Androgen Receptor Supports an Anchorage-Independent, Cancer Stem Cell-like Population in Triple-Negative Breast Cancer  
Valerie N. Barton, Jessica L. Christenson, Michael A. Gordon, Lisa I. Greene, Thomas J. Rogers, Kiel Butterfield, Beatrice Babbs, Nicole S. Spoelstra, Nicholas C. D'Amato, Anthony Elias, and Jennifer K. Richer  
*Précis:* These mechanistic studies demonstrate that androgen receptor–targeting therapies may empower chemotherapy in triple-negative breast cancers by targeting drug-resistant cancer stem-like cells.

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**3467** Mismatch Repair Proteins Initiate Epigenetic Alterations during Inflammation-Driven Tumorigenesis

Ashley R. Maiuri, Michael Peng, Ram Podicheti, Shruthi Sriramkumar, Caitlin M. Kamplain, Douglas B. Rusch, Christina E. DeStefano Shields, Cynthia L. Sears, and Heather M. O'Hagan

*Précis:* MSH2 is required for recruitment of epigenetic proteins to damaged chromatin and for DNA hypermethylation-mediated alterations in inflammation-induced tumors.

## THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

**3479** Targetable T-type Calcium Channels Drive Glioblastoma

Ying Zhang, Nichola Cruickshanks, Fang Yuan, Baomin Wang, Mary Pabuski, Julia Wulfkuhle, Isela Gallagher, Alexander F. Koeppl, Sarah Hatef, Christopher Papanicolas, Jeongwu Lee, Eli E. Bar, David Schiff, Stephen D. Turner, Emanuel F. Petricoin, Lloyd S. Gray, and Roger Abounader

*Précis:* This potentially seminal study provides a preclinical proof of concept for repurposing the FDA-approved drug mibefradil as a mechanism-based treatment for deadly glioblastomas.

**3491** Monitoring Tumor Response to Antivascular Therapy Using Non-Contrast Intravoxel Incoherent Motion Diffusion-Weighted MRI

Changzheng Shi, Dexiang Liu, Zeyu Xiao, Dong Zhang, Guanfu Liu, Guanshu Liu, Hanwei Chen, and Liangping Luo

*Précis:* These findings highlight advantages of a novel noninvasive imaging technique that can be used to predict efficacy of antivascular therapies, without the need for contrast media.

**3502** Engineering and Functional Characterization of Fusion Genes Identifies Novel Oncogenic Drivers of Cancer

Hengyu Lu, Nicole Villafane, Turgut Dogruluk, Caitlin L. Grzeskowiak, Kathleen Kong, Yiu Huen Tsang, Oksana Zagorodna, Angeliki Pantazi, Lixing Yang, Nicholas J. Neill, Young Won Kim, Chad J. Creighton, Roel G. Verhaak, Gordon B. Mills, Peter J. Park, Raju Kucherlapati, and Kenneth L. Scott

*Précis:* High-throughput construction of fusion genes often found in tumors facilitates more rapid functional tests to select optimal therapies directed against these genes.

**3513** Inhibition of Mitochondrial Matrix Chaperones and Antiapoptotic Bcl-2 Family Proteins Empower Antitumor Therapeutic Responses

Georg Karpel-Massler, Chiaki Tsuge Ishida, Elena Bianchetti, Chang Shu, Rolando Perez-Lorenzo, Basil Horst, Matei Banu, Kevin A. Roth, Jeffrey N. Bruce, Peter Canoll, Dario C. Altieri, and Markus D. Siegelin

*Précis:* This study offers a preclinical proof of concept for the combination of BH3 mimetic drugs and mitochondrial chaperone inhibitors as an effective therapeutic strategy for better management of drug-resistant tumors.

**3527** Targeting FBW7 as a Strategy to Overcome Resistance to Targeted Therapy in Non-Small Cell Lung Cancer



Mingxiang Ye, Yong Zhang, Xinxin Zhang, Jianbin Zhang, Pengyu Jing, Liang Cao, Nan Li, Xia Li, Libo Yao, Jian Zhang, and Jian Zhang

*Précis:* FBW7 downregulations stabilize the antiapoptotic BCL-2 family member MCL-1, unveiling a new mechanism of resistance to targeted therapeutics in the most common form of lung cancer.

**3540** Immune-Related Gene Expression Profiling After PD-1 Blockade in Non-Small Cell Lung Carcinoma, Head and Neck Squamous Cell Carcinoma, and Melanoma

Alex Prat, Alejandro Navarro, Laia Paré, Noemí Reguart, Patricia Galván, Tomás Pascual, Alex Martínez, Paolo Nuciforo, Laura Comerma, Lluçia Alos, Nuria Pardo, Susana Cedrés, Cheng Fan, Joel S. Parker, Lydia Gaba, Iván Victoria, Nuria Viñolas, Ana Vivancos, Ana Arance, and Enriqueta Felip

*Précis:* These results argue that a pre-existing stable adaptive immune response is sufficient to predict a clinical outcome, regardless of the type of cancer or a PD-1 therapeutic antibody administered to patients.

**3551** EGFR Mediates Responses to Small-Molecule Drugs Targeting Oncogenic Fusion Kinases

Aria Vaishnavi, Laura Schubert, Uwe Rix, Lindsay A. Marek, Anh T. Le, Stephen B. Keysar, Magdalena J. Glogowska, Matthew A. Smith, Severine Kako, Natalia J. Sumi, Kurtis D. Davies, Kathryn E. Ware, Marileila Varella-Garcia, Eric B. Haura, Antonio Jimeno, Lynn E. Heasley, Dara L. Aisner, and Robert C. Doebele

*Précis:* These findings show how previously unknown EGFR signaling mechanisms confer a critical survival mechanism to enable evasion from oncogene-specific inhibitors, providing a rationale to cotarget EGFR to reduce risks of developing drug resistance.

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**3564** The National Cancer Institute ALMANAC: A Comprehensive Screening Resource for the Detection of Anticancer Drug Pairs with Enhanced Therapeutic Activity

Susan L. Holbeck, Richard Camalier, James A. Crowell, Jeevan Prasaad Govindharajulu, Melinda Hollingshead, Lawrence W. Anderson, Eric Polley, Larry Rubinstein, Apurva Srivastava, Deborah Wilsker, Jerry M. Collins, and James H. Doroshow

*Précis:* This study describes a validated web-based resource to identify promising combinations of approved drugs with anticancer activity for further mechanistic study and translation to clinical trials.

## MICROENVIRONMENT AND IMMUNOLOGY

**3577** Chimeric PD-1:28 Receptor Upgrades Low-Avidity T cells and Restores Effector Function of Tumor-Infiltrating Lymphocytes for Adoptive Cell Therapy



Ramona Schlenker, Luis Felipe Olguín-Contreras, Matthias Leisegang, Julia Schnappinger, Anja Disovic, Svenja Rühland, Peter J. Nelson, Heinrich Leonhardt, Hartmann Harz, Susanne Wilde, Dolores J. Schendel, Wolfgang Uckert, Gerald Willimsky, and Elfriede Noessner

*Précis:* This study illustrates a method to empower adoptive T-cell therapies by engineering higher avidities that can improve effector function without sacrificing specificity.

**3591** Epstein–Barr Virus-Induced VEGF and GM-CSF Drive Nasopharyngeal Carcinoma Metastasis via Recruitment and Activation of Macrophages



Di Huang, Shi-Jian Song, Zi-Zhao Wu, Wei Wu, Xiu-Ying Cui, Jia-Ning Chen, Mu-Sheng Zeng, and Shi-Cheng Su

*Précis:* These findings define a feed-forward loop between virally infected nasopharyngeal cancer cells and macrophages and show how metastatic potential can evolve concurrently with virus-induced chronic inflammation.

**3605** Tumor-Associated Macrophages Promote Malignant Progression of Breast Phyllodes Tumors by Inducing Myofibroblast Differentiation

Yan Nie, Jianing Chen, Di Huang, Yandan Yao, Jiewen Chen, Lin Ding, Jiayi Zeng, Shicheng Su, Xue Chao, Fengxi Su, Herui Yao, Hai Hu, and Erwei Song

*Précis:* In establishing how tumor-associated macrophages drive myofibroblast differentiation and malignant progression of a type of stromal breast tumor, this study uncovers a series of potential therapeutic targets for its treatment.

**3619** STING Activation Reverses Lymphoma-Mediated Resistance to Antibody Immunotherapy

Lekh N. Dahal, Lang Dou, Khiyam Hussain, Rena Liu, Alexander Earley, Kerry L. Cox, Salome Murinello, Ian Tracy, Francesco Forconi, Andrew J. Steele, Patrick J. Duriez, Diego Gomez-Nicola, Jessica L. Teeling, Martin J. Glennie, Mark S. Cragg, and Stephen A. Beers

*Précis:* These findings suggest that STING agonists can empower monoclonal antibody therapies by reprogramming tumor-associated macrophages and curbing locoregional immunosuppression in the tumor microenvironment.

**3632** Deletion of Lactate Dehydrogenase-A in Myeloid Cells Triggers Antitumor Immunity

Pankaj Seth, Eva Csizmadia, Andreas Hedblom, Marta Vuerich, Han Xie, Mailin Li, Maria Serena Longhi, and Barbara Wegiel

*Précis:* Lactate dehydrogenase-A in the tumor microenvironment is a key determinant of immune responses against cancer and as such may provide a therapeutic target to blunt locoregional immune escape in tumors.

**3644** Sarcoma Eradication by Doxorubicin and Targeted TNF Relies upon CD8<sup>+</sup> T-cell Recognition of a Retroviral Antigen

Philipp Probst, Janine Kopp, Annette Oxenius, Mario P. Colombo, Danilo Ritz, Tim Fugmann, and Dario Neri

*Précis:* These findings offer evidence that retroviral genes contribute to tumoral immune surveillance through a process that can be improved by treatment with a TNF derivative and the chemotherapeutic drug doxorubicin.

**3655** CXCL1 Is Critical for Premetastatic Niche Formation and Metastasis in Colorectal Cancer

Dingzhi Wang, Haiyan Sun, Jie Wei, Bo Cen, and Raymond N. DuBois

*Précis:* These findings show how VEGFA induces production of the neutrophil chemoattractant CXCL1 in primary tumor macrophages, driving myeloid-derived suppressor cells to generate a premetastatic niche that enables later metastasis.

**3666** Landscape of Combination Immunotherapy and Targeted Therapy to Improve Cancer Management

Leandro M. Colli, Mitchell J. Machiela, Han Zhang, Timothy A. Myers, Lea Jessop, Olivier Delattre, Kai Yu, and Stephen J. Chanock

*Précis:* A survey of genomic profiles from public databases indicate that 8.9% of solid tumor patients could benefit from combinations of immunotherapy and targeted therapy, an approach that might significantly impact overall patient survival.

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**3672** Expansion of Tumor-Infiltrating CD8<sup>+</sup> T cells Expressing PD-1 Improves the Efficacy of Adoptive T-cell Therapy

Sarita M. Fernandez-Poma, Diego Salas-Benito, Teresa Lozano, Noelia Casares, Jose-Ignacio Riezu-Boj, Uxua Mancheño, Edurne Elizalde, Diego Alignani, Natalia Zubeldia, Itziar Otano, Enrique Conde, Pablo Sarobe, Juan Jose Lasarte, and Sandra Hervas-Stubbs

*Précis:* The antitumor activity of adoptive T-cell therapy is limited by low rates of ex vivo expansion of the highly differentiated PD-1<sup>+</sup> CD8 TIL population, which is responsible for the majority of tumor cell recognition in bulk CD8 TIL.

**3685** Persistent Immune Stimulation Exacerbates Genetically Driven Myeloproliferative Disorders via Stromal Remodeling



Claudio Tripodo, Alessia Burocchi, Pier Paolo Piccaluga, Claudia Chiodoni, Paola Portararo, Barbara Cappetti, Laura Botti, Alessandro Gulino, Alessandro Isidori, Arcangelo Liso, Giuseppe Visani, Maria Paola Martelli, Brunangelo Falini, Pier Paolo Pandolfi, Mario P. Colombo, and Sabina Sangaletti

*Précis:* Formation of neutrophil extracellular traps (NET) composed of DNA-protein complexes in the bone marrow tissue microenvironment stimulates the expansion of myeloid precursor cells, which support a certain class of human leukemias.

## PREVENTION AND EPIDEMIOLOGY

**3700** Beta-Blocker Drug Use and Survival among Patients with Pancreatic Adenocarcinoma

Ruzan Udumyan, Scott Montgomery, Fang Fang, Henrik Almroth, Unnur Valdimarsdottir, Anders Ekblom, Karin E. Smedby, and Katja Fall

*Précis:* These results suggest the repositioning of beta-blocker drugs, which are used widely to control hypertension and cardiac arrhythmias, to improve the survival of pancreatic cancer patients.

**3708** Assessment of Breast Cancer Risk Factors Reveals Subtype Heterogeneity

Johanna Holm, Louise Eriksson, Alexander Ploner, Mikael Eriksson, Mattias Rantalainen, Jingmei Li, Per Hall, and Kamila Czene

*Précis:* Breast cancer risk factors differ by molecular subtype, supporting distinct etiologies and offering implications for prevention studies, which rely on modeling risk prediction.

## RETRACTION

**3718** Retraction: Molecular Mechanism of MART-1<sup>+</sup>/A\*0201<sup>+</sup> Human Melanoma Resistance to Specific CTL-Killing Despite Functional Tumor-CTL Interaction

## CORRECTIONS

**3719** Correction: Rescue of p53 Function by Small-Molecule RITA in Cervical Carcinoma by Blocking E6-Mediated Degradation

**3720** Correction: Epigenetic Switch between SOX2 and SOX9 Regulates Cancer Cell Plasticity

**3721** Correction: Genetic Disruption of the Multifunctional CD98/LAT1 Complex Demonstrates the Key Role of Essential Amino Acid Transport in the Control of mTORC1 and Tumor Growth

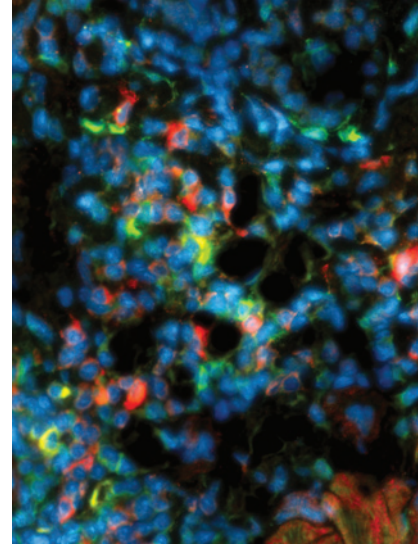
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## ABOUT THE COVER

Immunometabolism is emerging as a critical determinant of cancer pathophysiology. A balance between tumor promotion and elimination is dependent on the state of functional polarization of macrophage populations within the tumor microenvironment. Lactic acid generated by lactate dehydrogenase-A is a key metabolite that facilitates the immunosuppressive tumor microenvironment. Deletion of lactate dehydrogenase-A in myeloid cells restores the immunocompetent tumor microenvironment by reversing macrophage phenotype and antitumor immunity. Immunofluorescence staining revealed an increased number of infiltrating inducible nitric oxide synthase-positive (red) and M1-skewed F4.80-positive (green) macrophages in K-Ras tumors after deletion of lactate dehydrogenase-A. For details, see article by Seth and colleagues on page 3632.



# Cancer Research

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