

BREAKING ADVANCES

- 6735 **Highlights from Recent Cancer Literature**


REVIEWS

- 6737 **Thirty Years of Research on Met Receptor to Move a Biomarker from Bench to Bedside**
Alessandro Furlan, Zoulika Kherrouche, Rémi Montagne, Marie-Christine Copin, and David Tulasne
- 6745 **The Inherent Premise of Immunotherapy for Cancer Dormancy**
Masoud H. Manjili
- 6750 **Metastases in Immune-Mediated Dormancy: A New Opportunity for Targeting Cancer**
Irene Romero, Federico Garrido, and Angel M. Garcia-Lora

MICROENVIRONMENT AND IMMUNOLOGY

- 6758 **EGFR Activation and Signaling in Cancer Cells Are Enhanced by the Membrane-Bound Metalloprotease MT4-MMP**
Alexandra Paye, Alice Truong, Cassandre Yip, Jonathan Cimino, Silvia Blacher, Carine Munaut, Didier Cataldo, Jean Michel Foidart, Erik Maquoi, Joelle Collignon, Philippe Delvenne, Guy Jerusalem, Agnès Noel, and Nor Eddine Sounni
Précis: This important study identifies a positive modifier pathway for EGFR signaling that is likely to have wide impact and use as a theranostic biomarker in the many human cancers that involve EGFR activation.
- 6771 **CD47 in the Tumor Microenvironment Limits Cooperation between Antitumor T-cell Immunity and Radiotherapy**
David R. Soto-Pantoja, Masaki Terabe, Arunima Ghosh, Lisa A. Ridnour, William G. DeGraff, David A. Wink, Jay A. Berzofsky, and David D. Roberts
Précis: These findings establish that blocking the immunosuppressive molecule CD47 on cytotoxic T cells can enhance antitumor immunity in the context of radiotherapy, with the potential to increase curative radiation responses.

- 6784 **MHC-Restricted Phosphopeptides from Insulin Receptor Substrate-2 and CDC25b Offer Broad-Based Immunotherapeutic Agents for Cancer**
Angela L. Zarling, Rebecca C. Obeng, A. Nicole Desch, Joel Pinczewski, Kara L. Cummings, Donna H. Deacon, Mark Conaway, Craig L. Slingsluff Jr, and Victor H. Engelhard
Précis: This study characterizes two phosphopeptide antigens expressed on multiple types of solid tumors, defining them as candidate agents for broad-based cancer immunotherapy.

- 6796 **Efficacy of CAR T-cell Therapy in Large Tumors Relies upon Stromal Targeting by IFN γ**
 Ana Textor, Joanna J. Listopad, Lara Le Wührmann, Cynthia Perez, Anna Kruschinski, Markus Chmielewski, Hinrich Abken, Thomas Blankenstein, and Jehad Charo
Précis: This preclinical study shows how the inability of engineered T-cell therapies to eradicate solid tumors can be overcome by enabling antigen-independent stroma destruction along with antigen-specific tumor cell targeting, providing insights into ways to dramatically expand the utility of these therapies beyond circulating blood tumors, where they are currently useful.

- 6806 **Cancer-Associated Adipose Tissue Promotes Breast Cancer Progression by Paracrine Oncostatin M and Jak/STAT3 Signaling**
Lore Lapeire, An Hendrix, Kathleen Lambein, Mieke Van Bockstal, Geert Braems, Rudy Van Den Broecke, Ridha Limame, Pieter Mestdagh, Jo Vandesompele, Christian Vanhove, Dawn Maynard, Camille Lehuédé, Catherine Muller, Philippe Valet, Christian P. Gespach, Marc Bracke, Veronique Cocquyt, Hannelore Denys, and Olivier De Wever
Précis: Adipose tissue is an important contributor to breast cancer progression, but the mediators and mechanisms are not well enough understood to provide targeting strategies for therapeutic intervention in breast cancer patients.

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- 6820** **I T P R 1 Protects Renal Cancer Cells against Natural Killer Cells by Inducing Autophagy**
Yosra Messai, Muhammad Zaeem Noman, Meriem Hasmin, Bassam Janji, Andrés Tittarelli, Marie Boutet, Véronique Baud, Elodie Viry, Katy Billot, Arash Nanbakhsh, Thouraya Ben Safta, Catherine Richon, Sophie Ferlicot, Emmanuel Donnadieu, Sophie Couve, Betty Gardie, Florence Orlanducci, Laurence Albiges, Jerome Thiery, Daniel Olive, Bernard Escudier, and Salem Chouaib

Précis: Findings define a novel HIF2 α signaling axis that promotes immune escape from natural killer cells, providing a mechanistic understanding of how VHL-mutated kidney cancers defeat immune surveillance.

- 6833** **TGF β Receptor 1: An Immune Susceptibility Gene in HPV-Associated Cancer**
Chaya Levovitz, Dan Chen, Emma Ivansson, Ulf Gyllensten, John P. Finnigan, Sara Alshawish, Weijia Zhang, Eric E. Schadt, Marshal R. Posner, Eric M. Genden, Paolo Boffetta, and Andrew G. Sikora

Précis: Better understanding of the immunogenetic basis of susceptibility to HPV-associated cancers may offer insight into immune processes that are dysregulated in the minority of HPV-exposed individuals who develop cancer.

- 6845** **Inhibition of Adaptive Immunity by IL9 Can Be Disrupted to Achieve Rapid T-cell Sensitization and Rejection of Progressive Tumor Challenges**
Dominique B. Hoelzinger, Ana Lucia Dominguez, Peter A. Cohen, and Sandra J. Gendler

Précis: These results provide a compelling rationale to target the tolerogenic cytokine IL9, defined here as a checkpoint inhibitor of adaptive immunity that promotes immune escape to growing tumors by obscuring immunologic memory, as a unique new tool for cancer immunotherapy.

- 6856** **Globo-H Ceramide Shed from Cancer Cells Triggers Translin-Associated Factor X-Dependent Angiogenesis**
Jing-Yan Cheng, Sheng-Hung Wang, Juway Lin, Yi-Chien Tsai, John Yu, Jen-Chine Wu, Jung-Tung Hung, Jin-Jin Lin, Yih-Yiing Wu, Kun-Tu Yeh, and Alice L. Yu

Précis: An immune-suppressive ceramide lipid is transferred by exosome release from tumor cells to endothelial cells, where it strongly stimulates tumor angiogenesis, highlighting its importance as a therapeutic target related to tumor cell metabolism but also immune escape and angiogenesis in the tumor microenvironment.

MOLECULAR AND CELLULAR PATHOBIOLOGY

- 6867** **Alterations of Choline Phospholipid Metabolism in Endometrial Cancer Are Caused by Choline Kinase Alpha Overexpression and a Hyperactivated Deacylation Pathway**

Sebastian Trousil, Patrizia Lee, David J. Pinato, James K. Ellis, Roberto Dina, Eric O. Aboagye, Hector C. Keun, and Rohini Sharma

Précis: These results validate deregulated choline biochemistry as an important source of noninvasive imaging biomarkers for endometrial (uterine) cancers, for use in PET- or MRI-based imaging methods for diagnosis and treatment surveillance.

- 6878** **CD98hc (SLC3A2) Loss Protects Against Ras-Driven Tumorigenesis by Modulating Integrin-Mediated Mechanotransduction**
Soline Estrach, Sin-Ae Lee, Etienne Boulter, Sabrina Pisano, Aurélie Errante, Floriane S. Tissot, Laurence Cailleateau, Catherine Pons, Mark H. Ginsberg, and Chloé C. Féral

Précis: These results suggest a new function for the heavy subunit (CD98hc) of the large neutral amino acid transporter (LAT1), a cell surface protein overexpressed by many cancer cells, in stiffening the tumor microenvironment and altering cellular responses to it in a way that promotes malignant progression.

- 6890** **Long Noncoding RNA GAPLINC Regulates CD44-Dependent Cell Invasiveness and Associates with Poor Prognosis of Gastric Cancer**

Ye Hu, Jilin Wang, Jin Qian, Xuan Kong, JiETING Tang, Yingchao Wang, Haoyan Chen, Jie Hong, Weiping Zou, Yingxuan Chen, Jie Xu, and Jing-Yuan Fang

Précis: This study is the first to define a long noncoding RNA that regulates the CD44 oncogene, with potential implications for the prognosis and treatment of cancer.

- 6903** **Selective *In Vivo* Imaging of Syngeneic, Spontaneous, and Xenograft Tumors Using a Novel Tumor Cell-Specific Hsp70 Peptide-Based Probe**

Stefan Stangl, Julia Varga, Bianca Freysoldt, Marija Trajkovic-Arsic, Jens T. Siveke, Florian R. Greten, Vasilis Ntziachristos, and Gabriele Multhoff

Précis: This study offers preclinical validation of a highly specific tumor cell surface probe for noninvasive imaging of primary tumors and metastases, with potential applications in clinical diagnosis, therapeutic monitoring, and tumor-specific drug delivery.

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6913 **Common Genetic Variants in *NEFL* Influence Gene Expression and Neuroblastoma Risk**

Mario Capasso, Sharon Diskin, Flora Cimmino, Giovanni Acierno, Francesca Totaro, Giuseppe Petrosino, Lucia Pezone, Maura Diamond, Lee McDaniel, Hakon Hakonarson, Achille Iolascon, Marcella Devoto, and John M. Maris

Précis: *These results show that common variants in a neurofilament-like gene influence the susceptibility to neuroblastoma, providing genetic evidence of its role as a tumor suppressor in this deadly pediatric tumor.*

6925 **The Polyamine Catabolic Enzyme SAT1 Modulates Tumorigenesis and Radiation Response in GBM**

Adina Brett-Morris, Bradley M. Wright, Yuji Seo, Vinay Pasupuleti, Junran Zhang, Jun Lu, Raffaella Spina, Eli E. Bar, Maneesh Gujrati, Rebecca Schur, Zheng-Rong Lu, and Scott M. Welford

Précis: *Elevation of a polyamine acetyltransferase in deadly brain tumors contributes to their inherent radioresistance, with implications for targeting of this enzyme to improve radiotherapeutic responses in this setting.*

6935 **SCP Phosphatases Suppress Renal Cell Carcinoma by Stabilizing PML and Inhibiting mTOR/HIF Signaling**

Yu-Ching Lin, Li-Ting Lu, Hsin-Yi Chen, Xueyan Duan, Xia Lin, Xin-Hua Feng, Ming-Jer Tang, and Ruey-Hwa Chen

Précis: *These results define a novel pathway of PML degradation in a deadly kidney cancer, offering a mechanistic rationale for combination therapies that jointly target PML degradation and block mTOR activity for treatment.*

6947 **Nuclear Factor of Activated T-cell Activity Is Associated with Metastatic Capacity in Colon Cancer**



Manish K. Tripathi, Natasha G. Deane, Jing Zhu, Hanbing An, Shinji Mima, Xiaojing Wang, Sekhar Padmanabhan, Zhiao Shi, Naresh Prodduturi, Kristen K. Ciombor, Xi Chen, M. Kay Washington, Bing Zhang, and R. Daniel Beauchamp

Précis: *NFAT transcriptional targets constitute a straightforward expression signature to identify colon cancers with high risk of metastatic recurrence.*

PREVENTION AND EPIDEMIOLOGY

6958 **Early Pregnancy Sex Steroids and Maternal Breast Cancer: A Nested Case-Control Study**

Renée T. Fortner, Helena Schock, Rudolf Kaaks, Matti Lehtinen, Eero Pukkala, Hans-Åke Lakso, Minna Tanner, Raija Kallio, Heikki Joensuu, Kjell Grankvist, Anne Zeleniuch-Jacquotte, Paolo Toniolo, Eva Lundin, and Helja-Marja Surcel

Précis: *These findings come from the first investigation of how sex steroid hormone exposure during early pregnancy affects subsequent risk of breast cancer in the mother, by tumor hormone receptor status.*

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

6968 **ATR Inhibitors VE-821 and VX-970 Sensitize Cancer Cells to Topoisomerase I Inhibitors by Disabling DNA Replication Initiation and Fork Elongation Responses**

Rozenn Jossé, Scott E. Martin, Rajarshi Guha, Pinar Ormanoglu, Thomas D. Pfister, Philip M. Reaper, Christopher S. Barnes, Julie Jones, Peter Charlton, John R. Pollard, Joel Morris, James H. Doroshow, and Yves Pommier

Précis: *By showing how the DNA damage sensing kinase ATR confers resistance to topoisomerase I inhibitors, a widely used class of cytotoxic drugs in the oncology clinic, this study provides a mechanistic rationale for combination trials to evaluate the efficacy of ATR inhibitors.*

6980 **Patient-Derived Ovarian Tumor Xenografts Recapitulate Human Clinicopathology and Genetic Alterations**

Francesca Ricci, Francesca Bizzaro, Marta Cesca, Federica Guffanti, Monica Ganzinelli, Alessandra Decio, Carmen Ghilardi, Patrizia Perego, Robert Fruscio, Alessandro Buda, Rodolfo Milani, Paola Ostano, Giovanna Chiorino, Maria Rosa Bani, Giovanna Damia, and Raffaella Giavazzi

Précis: *Accurate clinicopathologic and molecular features of ovarian tumors that have never seen a tissue culture dish are preserved in mouse xenograft models that may provide superior tools to develop therapeutic modalities.*

6991 **Long-Chain Fatty Acid Analogues Suppress Breast Tumorigenesis and Progression**

Udi Gluschnaider, Rachel Hertz, Sarit Ohayon, Elia Smeir, Martha Smets, Eli Pikarsky, and Jacob Bar-Tana

Précis: *Fatty acid-like drugs with antidiabetic effects may offer therapeutic potential in breast cancer patients, also addressing the generally poor compliance of obese patients with restriction of carbohydrates in their diet.*

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7003 **Preclinical Activity of Nanoliposomal Irinotecan Is Governed by Tumor Deposition and Intratumor Prodrug Conversion**



Ashish V. Kalra, Jaeyeon Kim, Stephan G. Klinz, Nancy Paz, Jason Cain, Daryl C. Drummond, Ulrik B. Nielsen, and Jonathan B. Fitzgerald

Précis: Liposomal encapsulation of irinotecan can safely improve its antitumor activity in preclinical models by enhancing deposition and intratumoral activation of the prodrug within the tumor microenvironment.

7014 **NGF Blockade at Early Times during Bone Cancer Development Attenuates Bone Destruction and Increases Limb Use**

Gwen McCaffrey, Michelle L. Thompson, Lisa Majuta, Michelle N. Fealk, Stephane Chartier, Geraldine Longo, and Patrick W. Mantyh

Précis: This important preclinical study shows how administration of antibodies against nerve growth factor as soon as bone metastasis is detected can reduce bone pain and destruction and help preserve limb use, with immediate implications for clinical evaluation in patients with metastatic bone disease.

7024 **Hedgehog Signaling Drives Radioresistance and Stroma-Driven Tumor Repopulation in Head and Neck Squamous Cancers**

Gregory N. Gan, Justin Eagles, Stephen B. Keysar, Guoliang Wang, Magdalena J. Glogowska, Cem Altunbas, Ryan T. Anderson, Phuong N. Le, J. Jason Morton, Barbara Frederick, David Raben, Xiao-Jing Wang, and Antonio Jimeno

Précis: These findings offer a mechanistic rationale for the use of Hedgehog signaling inhibitors as radiosensitizers in head and neck cancers, which are widely resistant to radiotherapy, with immediate implications for clinical evaluation.

7037 **Inhibition of mTORC1/2 Overcomes Resistance to MAPK Pathway Inhibitors Mediated by PGC1 α and Oxidative Phosphorylation in Melanoma**

Y.N. Vashisht Gopal, Helen Rizos, Guo Chen, Wanleng Deng, Dennie T. Frederick, Zachary A. Cooper, Richard A. Scolyer, Gulietta Pupo, Kakajan Komurov, Vasudha Sehgal, Jiexin Zhang, Lalit Patel, Cristiano G. Pereira, Bradley M. Broom, Gordon B. Mills, Prahlad Ram, Paul D. Smith, Jennifer A. Wargo, Georgina V. Long, and Michael A. Davies

Précis: These findings highlight the significance of oxidative phosphorylation to drug resistance in melanoma and suggest that combined targeting of the MAPK and mTORC pathways may offer an effective strategy to treat melanomas with this metabolic phenotype.

7048 **Targeting the MYC and PI3K Pathways Eliminates Leukemia-Initiating Cells in T-cell Acute Lymphoblastic Leukemia**

Suzanne Schubbert, Anjelica Cardenas, Harrison Chen, Consuelo Garcia, Wei Guo, James Bradner, and Hong Wu

Précis: These findings define critical events that may be targeted to eliminate cancer stem-like cells in T-ALL as a new strategy to treat the most aggressive relapsed forms of this disease.

7060 **Molecular Modulation of Estrogen-Induced Apoptosis by Synthetic Progestins in Hormone Replacement Therapy: An Insight into the Women's Health Initiative Study**

Elizabeth E. Sweeney, Ping Fan, and V. Craig Jordan

Précis: These findings provide a molecular explanation for the increase in breast cancer risk observed in postmenopausal women taking hormone replacement therapy (HRT) and suggest a change in prescribing HRT.

7069 **Chemotherapeutic Agents Subvert Tumor Immunity by Generating Agonists of Platelet-Activating Factor**

Ravi P. Sahu, Jesus A. Ocana, Kathleen A. Harrison, Matheus Ferracini, Christopher E. Touloukian, Mohammed Al-Hassani, Louis Sun, Mathew Loesch, Robert C. Murphy, Sandra K. Althouse, Susan M. Perkins, Paul J. Speicher, Douglas S. Tyler, Raymond L. Konger, and Jeffrey B. Travers

Précis: This study shows how chemotherapeutic agents can suppress antitumor immunity by activating platelets, with implications for improving chemotherapeutic efficacy by coordinate blockade of this pathway.

7079 **ERK Mutations Confer Resistance to Mitogen-Activated Protein Kinase Pathway Inhibitors**

Eva M. Goetz, Mahmoud Ghandi, Daniel J. Treacy, Nikhil Wagle, and Levi A. Garraway

Précis: Identification of ERK1/2 mutations may provide insights for resistance to therapies targeting this pathway.

TUMOR AND STEM CELL BIOLOGY

7090 **BET Protein Inhibitor JQ1 Attenuates Myc-Amplified MCC Tumor Growth *In Vivo***



Qiang Shao, Aarthi Kannan, Zhenyu Lin, Brendan C. Stack Jr, James Y. Suen, and Ling Gao

Précis: These results provide a preclinical proof of concept to evaluate inhibitors of a bromodomain-containing chromatin regulatory factor in clinical treatment of Merkel carcinoma, a rare disease in which c-Myc appears to be activated.

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- 7103** **CCR5 Receptor Antagonists Block Metastasis to Bone of v-Src Oncogene–Transformed Metastatic Prostate Cancer Cell Lines**
 Daniela Sicoli, Xuanmao Jiao, Xiaoming Ju, Marco Velasco-Velazquez, Adam Ertel, Sankar Addya, Zhiping Li, Sebastiano Andò, Alessandro Fatatis, Bishnuhari Paudyal, Massimo Cristofanilli, Mathew L. Thakur, Michael P. Lisanti, and Richard G. Pestell
Précis: CCR5 antagonists, originally developed as HIV entry inhibitors, reduce invasiveness and metastatic capability of prostate cancer cells to bone and brain, with immediate clinical implications for evaluation as antimetastatic drugs.
- 7115** **Changes in Pyruvate Metabolism Detected by Magnetic Resonance Imaging Are Linked to DNA Damage and Serve as a Sensor of Temozolomide Response in Glioblastoma Cells**
 Ilwoo Park, Joydeep Mukherjee, Motokazu Ito, Myriam M. Chaumeil, Llewellyn E. Jalbert, Karin Gaensler, Sabrina M. Ronen, Sarah J. Nelson, and Russell O. Pieper
Précis: This study shows how DNA damage caused by the chemotherapeutic drug temozolomide affects pyruvate metabolism, and how these metabolic changes can be exploited by MRI as an early sensor of therapeutic response.
- 7125** **HSP90 Supports Tumor Growth and Angiogenesis through PRKD2 Protein Stabilization**
Ninel Azoitei, Kristina Diepold, Cornelia Brunner, Arefeh Rouhi, Felicitas Genze, Alexander Becher, Hans Kestler, Johan van Lint, Gabriela Chiosis, John Koren III, Stefan Fröhling, Claudia Scholl, and Thomas Seufferlein
Précis: These findings indicate that oncogenic contributions of the kinase PRKD2 might be exploited to target particularly hypoxic tumors, with immediately actionable implications in the clinic with ongoing development of PRKD2 inhibitors.
- 7137** **Densely Ionizing Radiation Acts via the Microenvironment to Promote Aggressive Trp53-Null Mammary Carcinomas**
Irineu Illa-Bochaca, Haoxu Ouyang, Jonathan Tang, Christopher Sebastiano, Jian-Hua Mao, Sylvain V. Costes, Sandra Demaria, and Mary Helen Barcellos-Hoff
Précis: These mechanistic findings provide further evidence that microenvironmental changes from radiation contribute strongly to carcinogenic potential.
- 7149** **Distinct Luminal-Type Mammary Carcinomas Arise from Orthotopic Trp53-Null Mammary Transplantation of Juvenile versus Adult Mice**
David H. Nguyen, Haoxu Ouyang, Jian-Hua Mao, Lynn Hlatky, and Mary Helen Barcellos-Hoff
Précis: These results offer direct support for the notion that age-associated host physiology greatly influences the intrinsic subtype of breast cancer, with implications for prevention and treatment strategies in this setting.

 AC icon indicates Author Choice

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ABOUT THE COVER

The image shows a high resolution X-ray of a mouse hip and tumor-bearing mouse femur that was treated with anti-nerve growth antibody. Radiographs of the femur demonstrated that at day 28 postinjection of sarcoma cancer cells into the femur, early and sustained sequestration of nerve growth factor not only reduced bone cancer pain but attenuated sarcoma-induced bone destruction and delayed time to fracture. For details, see article by McCaffrey and colleagues on page 7014.

