

## BREAKING ADVANCES

- 4023** Highlights from Recent Cancer Literature

## CANCER RESEARCH 75TH ANNIVERSARY COMMENTARIES

- 4025** Colon Cancer Germline Genetics: The Unbelievable Year 1993 and Thereafter  
Albert de la Chapelle
- 4028** The Role of CagA in the Gastric Biology of *Helicobacter pylori*  
Steffen Backert and Martin J. Blaser


## REVIEW

- 4032** Efficacy and Mechanisms of Aerobic Exercise on Cancer Initiation, Progression, and Metastasis: A Critical Systematic Review of *In Vivo* Preclinical Data  
Kathleen A. Ashcraft, Ralph M. Peace, Allison S. Betof, Mark W. Dewhirst, and Lee W. Jones

## PRIORITY REPORT

- 4051** Adipocyte Exosomes Promote Melanoma Aggressiveness through Fatty Acid Oxidation: A Novel Mechanism Linking Obesity and Cancer  
Ikrame Lazar, Emily Clement, Stéphanie Dauvillier, Delphine Milhas, Manuelle Ducoux-Petit, Sophie LeGonidec, Cédric Moro, Vanessa Soldan, Stéphane Dalle, Stéphanie Balor, Muriel Golzio, Odile Burlet-Schiltz, Philippe Valet, Catherine Muller, and Laurence Nieto
- Précis:* These results reveal a mechanism that may help explain why obese cancer patients tend to have a poorer prognosis.

## INTEGRATED SYSTEMS AND TECHNOLOGIES

- 4058** Copy Number Alterations in Enzyme-Coding and Cancer-Causing Genes Reprogram Tumor Metabolism  
Ashwini Kumar Sharma, Roland Eils, and Rainer König  
*Précis:* This study reveals a hitherto unknown generic mechanism for large-scale metabolic reprogramming in cancer cells, based on linear gene proximities between cancer-causing and -metabolic genes, with the identification of 119 genes likely to be involved in rewiring cancer cell metabolism.
- 4068** Systematic Analysis of AU-Rich Element Expression in Cancer Reveals Common Functional Clusters Regulated by Key RNA-Binding Proteins  
 Edward Hitti, Tala Bakheet, Norah Al-Souhibani, Walid Moghrabi, Suhad Al-Yahya, Maha Al-Ghamdi, Maher Al-Saif, Mohamed M. Shoukri, András Lániczky, Renaud Grépin, Balázs Györfy, Gilles Pagès, and Khalid S.A. Khabar  
*Précis:* This study significantly expands the repertoire of cancer genes that are regulated by RNA stability proteins and how these interactions impact the cancer patient survival.
- 4081** VEGFR2-Targeted Three-Dimensional Ultrasound Imaging Can Predict Responses to Antiangiogenic Therapy in Preclinical Models of Colon Cancer  
Jianhua Zhou, Huaijun Wang, Huiping Zhang, Amelie M. Lutz, Lu Tian, Dimitre Hristov, and Jürgen K. Willmann  
*Précis:* A clinical ultrasound imaging system capable of predicting therapeutic responses to treatment with angiogenesis inhibitors may be valuable to predict patient outcomes.
- 4090** Survival of Patients with Gastrointestinal Cancers Can Be Predicted by a Surrogate microRNA Signature for Cancer Stem-like Cells Marked by DCLK1 Kinase  
Nathaniel Weygant, Yang Ge, Dongfeng Qu, John S. Kaddis, William L. Berry, Randal May, Parthasarathy Chandrakesan, Edwin Bannerman-Menson, Kenneth J. Vega, James J. Tomasek, Michael S. Bronze, Guangyu An, and Courtney W. Houchen  
*Précis:* These findings offer an initial guidepost toward the development of improved prognostic biomarkers or companion biomarkers for DCLK1-targeted therapies aimed at eradicating cancer stem-like cells in several GI malignancies.

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## MICROENVIRONMENT AND IMMUNOLOGY

### 4100 Rapalogs Efficacy Relies on the Modulation of Antitumor T-cell Immunity

Laurent Beziaud, Laura Mansi, Patrice Ravel, Elodie Lauret Marie-Joseph, Caroline Laheurte, Laurie Rangan, Francis Bonnefoy, Jean-René Pallandre, Laura Boullerot, Clémentine Gamonet, Sindy Vrecko, Lise Queiroz, Tristan Maurina, Guillaume Mouillet, Thierry Nguyen Tan Hon, Elsa Curtit, Bernard Royer, Béatrice Gaugler, Jagadeesh Bayry, Eric Tartour, Antoine Thiery-Vuillemin, Xavier Pivot, Christophe Borg, Yann Godet, and Olivier Adotévi

*Précis:* While mTOR inhibitors can paradoxically induce protective T-cell immunity in renal cancer, prolonged treatment in this setting creates immunosuppressive effects that might be reversed by immune checkpoint blockade.

### 4113 Immuno-PET Imaging of Engineered Human T Cells in Tumors

Sabine Mall, Nahid Yusufi, Ricarda Wagner, Richard Klar, Henrique Bianchi, Katja Steiger, Melanie Straub, Stefan Audehm, Iina Laitinen, Michaela Aichler, Christian Peschel, Sibylle Ziegler, Mona Mustafa, Markus Schwaiger, Calogero D'Alessandria, and Angela M. Krackhardt

*Précis:* These findings offer a preclinical proof of concept for a readily translatable method to image different distribution patterns of transgenic T cells used in adoptive transfer therapies for cancer patients.

### 4124 FAP Promotes Immunosuppression by Cancer-Associated Fibroblasts in the Tumor Microenvironment via STAT3–CCL2 Signaling

Xuguang Yang, Yuli Lin, Yinghong Shi, Bingji Li, Weiren Liu, Wei Yin, Yongjun Dang, Yiwei Chu, Jia Fan, and Rui He

*Précis:* These results illuminate how a subset of cancer-associated fibroblasts can be programmed to contribute to an inflammatory tumor microenvironment, a feature of possible great importance in desmoplasia-associated cancers.

### 4136 Upregulated Glucose Metabolism Correlates Inversely with CD8<sup>+</sup> T-cell Infiltration and Survival in Squamous Cell Carcinoma

Christian H. Ottensmeier, Kate L. Perry, Elena L. Harden, Jana Stasakova, Veronika Jenei, Jason Fleming, Oliver Wood, Jeongmin Woo, Christopher H. Woelk, Gareth J. Thomas, and Stephen M. Thirdborough

*Précis:* EGFR-driven tumor glycolysis is a major factor contributing to the lack of T-cell infiltration in squamous cell carcinoma, potentially contributing to immune escape.

## MOLECULAR AND CELLULAR PATHOBIOLOGY

### 4149 Early Epigenetic Downregulation of microRNA-192 Expression Promotes Pancreatic Cancer Progression



Sandeep K. Botla, Soniya Savant, Pouria Jandaghi, Andrea S. Bauer, Oliver Mücke, Evgeny A. Moskalev, John P. Neoptolemos, Eithne Costello, William Greenhalf, Aldo Scarpa, Matthias M. Gaida, Markus W. Büchler, Oliver Strobel, Thilo Hackert, Nathalia A. Giese, Hellmut G. Augustin, and Jörg D. Hoheisel

*Précis:* These provocative results suggest a mechanistic explanation for the very early metastatic behavior of pancreatic cancers, with implications for early diagnosis and therapy in this aggressive disease.

### 4160 miR-29b Mediates NF-κB Signaling in KRAS-Induced Non–Small Cell Lung Cancers

Stephanie Langsch, Ulrich Baumgartner, Stefan Haemmig, Cornelia Schlup, Stephan C. Schäfer, Sabina Berezowska, Gregor Rieger, Patrick Dorn, Mario P. Tschan, and Erik Vassella

*Précis:* These results reveal a complexity in cancer for miR-29b, which while ascribed a tumor suppressor role elsewhere, is found in this particular study of KRAS-mutant lung cancers to act as an oncogene that promotes apoptotic resistance.

### 4170 S-nitrosylation of the Mitochondrial Chaperone TRAP1 Sensitizes Hepatocellular Carcinoma Cells to Inhibitors of Succinate Dehydrogenase

Salvatore Rizza, Costanza Montagna, Simone Cardaci, Emiliano Maiani, Giuseppina Di Giacomo, Virginia Sanchez-Quiles, Blagoy Blagoev, Andrea Rasola, Daniela De Zio, Jonathan S. Stamler, Francesco Cecconi, and Giuseppe Filomeni

*Précis:* These findings probe a metabolic Achilles' heel in a certain genetic subclass of liver cancer, providing a preclinical rationale for a new strategy to attack this deadly disease.

### 4183 A Novel Chemotherapeutic Agent to Treat Tumors with DNA Mismatch Repair Deficiencies



Yongliang Zhang, Jennifer T. Fox, Young-Un Park, Gene Elliott, Ganesha Rai, Mengli Cai, Srilatha Sakamuru, Ruili Huang, Menghang Xia, Kyeryoung Lee, Min Ho Jeon, Bijoy P. Mathew, Hee Dong Park, Winfried Edelmann, Chan Young Park, Sung You Hong, David Maloney, and Kyungjae Myung

*Précis:* These findings offer a preclinical proof of concept for baicalein, a novel chemotherapeutic agent to treat up to 5% of colorectal tumors that are deficient for DNA mismatch repair.

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**4192** Histone Deacetylase Inhibition in Prostate Cancer Triggers miR-320–Mediated Suppression of the Androgen Receptor

Shinya Sato, Keisuke Katsushima, Keiko Shinjo, Akira Hatanaka, Fumiharu Ohka, Shugo Suzuki, Aya Naiki-Ito, Norihito Soga, Satoru Takahashi, and Yutaka Kondo

*Précis:* This important study describes a novel mechanism for downregulation of the androgen receptor, which efficiently suppresses the growth of prostate cancer, regardless of its hormone sensitivity.

**4205** Phenotypic and Signaling Consequences of a Novel Aberrantly Spliced Transcript FGF Receptor-3 in Hepatocellular Carcinoma



Ke Li, Baiyong Shen, Xi Cheng, Ding Ma, Xiaoqian Jing, Xinyu Liu, Weiping Yang, Chenghong Peng, and Weihua Qiu

*Précis:* Missplicing of FGFR3 in hepatocellular carcinoma contributes significantly to its malignant character, with potential implications for therapeutic targeting.

**4216** Novel  $\beta$ -HPV49 Transgenic Mouse Model of Upper Digestive Tract Cancer

Daniele Viarisio, Karin Müller-Decker, Paola Zanna, Ulrich Kloz, Birgit Aengeneyndt, Rosita Accardi, Christa Flechtenmacher, Lutz Gissmann, and Massimo Tommasino

*Précis:* These findings suggest the utility of little studied HPV strains in understanding tissue-specific mechanisms of carcinogenesis, which involve environmental risk factors.

## PREVENTION AND EPIDEMIOLOGY

**4226** Dietary Weight Loss and Exercise Effects on Serum Biomarkers of Angiogenesis in Overweight Postmenopausal Women: A Randomized Controlled Trial

Catherine Duggan, Jean de Dieu Tapsoba, Ching-Yun Wang, and Anne McTiernan

*Précis:* Weight loss is associated with reduced circulating markers of angiogenesis, suggesting an incentive to reduce weight as a cancer prevention method in overweight and obese individuals.

## THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

**4236** The E3-ligase E6AP Represses Breast Cancer Metastasis via Regulation of ECT2-Rho Signaling

Mariam Mansour, Sue Haupt, Ai-Leen Chan, Nathan Godde, Alexandra Rizzitelli, Sherene Loi, Franco Caramia, Siddhartha Deb, Elena A. Takano, Mark Bishton, Cameron Johnstone, Brendon Monahan, Yarra Levav-Cohen, Yong-Hui Jiang, Alpha S. Yap, Stephen Fox, Ora Bernard, Robin Anderson, and Ygal Haupt

*Précis:* These findings propose an E3 ligase-RhoGEF signaling axis as a candidate therapeutic target to block breast cancer metastasis, illustrating the possible selective benefits of therapies, which target Rho signaling in cancer cells.

**4249** Tumor Cell Invasion Can Be Blocked by Modulators of Collagen Fibril Alignment That Control Assembly of the Extracellular Matrix

Moran Grossman, Nir Ben-Chetrit, Alina Zhuravlev, Ran Afik, Elad Bassat, Inna Solomonov, Yosef Yarden, and Irit Sagi

*Précis:* This study shows how preventing the organization of abnormal architectures of collagen fiber in the extracellular matrix can effectively arrest the invasive behavior of malignant cells.

**4259** Definition of a Novel Feed-Forward Mechanism for Glycolysis-HIF1 $\alpha$  Signaling in Hypoxic Tumors Highlights Aldolase A as a Therapeutic Target



Geoffrey Grandjean, Petrus R. de Jong, Brian P. James, Mei Yee Koh, Robert Lemos, John Kingston, Alexander Aleshin, Laurie A. Bankston, Claudia P. Miller, Eun Jeong Cho, Ramakrishna Edupuganti, Ashwini Devkota, Gabriel Stancu, Robert C. Liddington, Kevin N. Dalby, and Garth Powis

*Précis:* This important study offers a preclinical rationale to develop inhibitors of the glycolytic enzyme aldolase A as a generalized strategy to treat intractable hypoxic cancer cells, which are found in most human solid tumors.

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## TUMOR AND STEM CELL BIOLOGY

**4270** Tissue Factor Induced by Epithelial–Mesenchymal Transition Triggers a Procoagulant State That Drives Metastasis of Circulating Tumor Cells

Morgane Bourcy, Meggy Suarez-Carmona, Justine Lambert, Marie-Emilie Francart, H el ene Schroeder, C eline Delieuneux, Nicolas Skrypek, Erik W. Thompson, Guy J erusalem, Geert Berx, Marc Thiry, Silvia Blacher, Brett G. Hollier, Agn es No el, C ecile Oury, Myriam Polette, and Christine Gilles

*Pr ecis:* These findings show how local activation of coagulation pathways in EMT-positive circulating tumor cells supports their metastatic colonization and spread, heightening the urgency for immediate clinical study of new anticoagulant drugs to prevent metastasis in cancer patients in remission after their initial treatment.

**4283** MFG-E8 Drives Melanoma Growth by Stimulating Mesenchymal Stromal Cell–Induced Angiogenesis and M2 Polarization of Tumor-Associated Macrophages

Kazuya Yamada, Akihiko Uchiyama, Akihito Uehara, Buddhini Perera, Sachiko Ogino, Yoko Yokoyama, Yuko Takeuchi, Mark C. Udey, Osamu Ishikawa, and Sei-ichiro Motegi

*Pr ecis:* A proangiogenic factor that helps bypass anti-VEGF therapy appears to act at two levels in the tumor microenvironment to promote angiogenesis, by affecting both mesenchymal stromal cells and tumor-associated macrophages.

**4293** miR-182-5p Induced by STAT3 Activation Promotes Glioma Tumorigenesis

Jianfei Xue, Aidong Zhou, Yamei Wu, Saint-Aaron Morris, Kangyu Lin, Samirkumar Amin, Roeland Verhaak, Gregory Fuller, Keping Xie, Amy B. Heimberger, and Suyun Huang

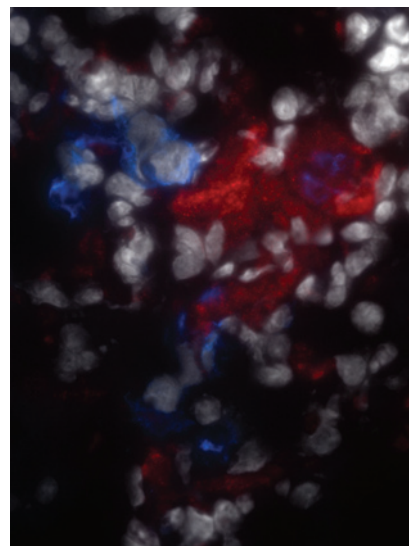
*Pr ecis:* Manipulating the microRNA-mediated tumor suppressor pathway described in this study may offer a novel therapeutic approach to treat glioblastoma, the deadliest brain cancer.

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## ABOUT THE COVER

Epithelial–mesenchymal transition induces tissue factor expression and coagulant properties that drive early metastasis of circulating tumor cells. Using immunofluorescence, vimentin-expressing tumor cells (red) surrounded by platelet-rich microthrombi (blue) were observed colonizing lungs in experimental models of metastasis (nuclei, white). For details, see article by Bourcy and colleagues on page 4270.



# Cancer Research

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