

BREAKING ADVANCES

- 2849** Highlights from Recent Cancer Literature

CANCER RESEARCH 75th ANNIVERSARY COMMENTARIES

- 2851** Commentary on Alfred G. Knudson, Jr.: "Hereditary Cancer, Oncogenes, and Antioncogenes"
Philip W. Hinds
- 2854** Commentary on Folkman: "How Is Blood Vessel Growth Regulated in Normal and Neoplastic Tissue?"
Hellmut G. Augustin

REVIEW

- 2857** The Widening Sphere of Influence of HOXB7 in Solid Tumors
Maria Cristina Errico, Kideok Jin, Saraswati Sukumar, and Alessandra Carè

MEETING REPORT

- 2863** Immunostimulatory Monoclonal Antibodies and Immunomodulation: Harvesting the Crop
Pedro Berraondo, María Carmen Ochoa, María Esperanza Rodríguez-Ruiz, Luna Minute, Juan José Lasarte, and Ignacio Melero

PRIORITY REPORTS


- 2868** Hyperthermia Synergizes with Chemotherapy by Inhibiting PARP1-Dependent DNA Replication Arrest
Lea Schaaf, Matthias Schwab, Christoph Ulmer, Simon Heine, Thomas E. Mürdter, Jens O. Schmid, Georg Sauer, Walter E. Aulitzky, and Heiko van der Kuip
Précis: Important mechanistic findings offer an explanation for the long-standing question why hyperthermia potentiates cytotoxic effects of chemotherapy and also open an avenue to replace hyperthermia by well-tolerated PARP inhibitors.

- 2876** Extracellular Vesicles from High-Grade Glioma Exchange Diverse Pro-oncogenic Signals That Maintain Intratumoral Heterogeneity
Franz Ricklefs, Marco Mineo, Arun K. Rooj, Ichiro Nakano, Al Charest, Ralph Weissleder, Xandra O. Breakefield, E. Antonio Chiocca, Jakub Godlewski, and Agnieszka Bronisz

Précis: Extracellular vesicles emitted by different tumor cell subtypes mediate dynamic interactions that may help maintain tumor heterogeneity, a phenomenon of all human cancers but few cancer models, a timely high concern in learning how tumor heterogeneity and its dynamics impact patient outcomes.

INTEGRATED SYSTEMS AND TECHNOLOGIES

- 2882** Mathematical Modeling Reveals That Changes to Local Cell Density Dynamically Modulate Baseline Variations in Cell Growth and Drug Response
James M. Greene, Doron Levy, Sylvia P. Herrada, Michael M. Gottesman, and Orit Lavi
Précis: Tracking the spatiotemporal process of cell growth reveals that heterogeneity in intrinsic cellular features relies upon the local microenvironment, which should be considered in assessing cellular responses to environmental stimuli.

- 2891** Hemolytic *E. coli* Promotes Colonic Tumorigenesis in Females
 Ye Jin, Senwei Tang, Weilin Li, Siew Chien Ng, Michael W.Y. Chan, Joseph J.Y. Sung, and Jun Yu
Précis: This study has immediate clinical implications in revealing that infection with a specific type of pathogenic *E. coli* is associated with increased colon tumorigenesis in females.

- 2901** miR-146b-5p within BCR-ABL1-Positive Microvesicles Promotes Leukemic Transformation of Hematopoietic Cells
Hong-Mei Zhang, Qing Li, Xiaojian Zhu, Wei Liu, Hui Hu, Teng Liu, Fanjun Cheng, Yong You, Zhaodong Zhong, Ping Zou, Qiubai Li, Zhichao Chen, and An-Yuan Guo
Précis: These findings reveal how a critical miRNA present in tumor microvesicles directs the malignant transformation of normal hematopoietic cells to a leukemic state.

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2912 Acetylcarnitine Is a Candidate Diagnostic and Prognostic Biomarker of Hepatocellular Carcinoma



Yonghai Lu, Ning Li, Liang Gao, Yong-Jiang Xu, Chong Huang, Kangkang Yu, Qingxia Ling, Qi Cheng, Shengsen Chen, Mengqi Zhu, Jinling Fang, Mingquan Chen, and Choon Nam Ong

Précis: In addressing the need of more sensitive and specific biomarkers for liver cancer progression and diagnosis, this study identifies a marker with a supplementary role to α -fetoprotein as it is currently used, particularly in HCC patients with low levels of this established marker.

MICROENVIRONMENT AND IMMUNOLOGY

2921 CD27 Agonism Plus PD-1 Blockade Recapitulates CD4⁺ T-cell Help in Therapeutic Anticancer Vaccination

Tomasz Ahrends, Nikolina Bąbala, Yanling Xiao, Hideo Yagita, Hans van Eenennaam, and Jannie Borst

Précis: While cancer vaccines offer appeal as therapeutic regimens, their utility must be optimized by overcoming immune suppressive mechanisms, which impede their efficacy.

2932 Hematopoietic Age at Onset of Triple-Negative Breast Cancer Dictates Disease Aggressiveness and Progression



Timothy Marsh, Irene Wong, Jaclyn Sceneay, Amey Barakat, Yuanbo Qin, Andreas Sjödin, Elise Alspach, Björn Nilsson, Sheila A. Stewart, and Sandra S. McAllister

Précis: These results elucidate the cellular mechanisms underlying the aggressiveness of triple-negative breast cancer in young women compared with older women, providing a rationale to investigate age-stratified therapies that in particular target the age-sensitive bone marrow microenvironment.

MOLECULAR AND CELLULAR PATHOBIOLOGY

2944 GPCR Signaling Mediates Tumor Metastasis via PI3K β

Bassem D. Khalil, Christine Hsueh, Yanyan Cao, Widian F. Abi Saab, Yarong Wang, John S. Condeelis, Anne R. Bresnick, and Jonathan M. Backer

Précis: Regulation of the phosphatidylinositol 3-kinase, PI3K β , by G protein-coupled receptor signaling is shown to be critical for tumor invasion and metastasis.

2954 The EGF Receptor Promotes the Malignant Potential of Glioma by Regulating Amino Acid Transport System xc(–)



Kenji Tsuchihashi, Shogo Okazaki, Mitsuyo Ohmura, Miyuki Ishikawa, Oltea Sampetean, Nobuyuki Onishi, Hiroaki Wakimoto, Momoko Yoshikawa, Ryo Seishima, Yoshimi Iwasaki, Takayuki Morikawa, Shinya Abe, Ayumi Takao, Misato Shimizu, Takashi Masuko, Motoo Nagane, Frank B. Furnari, Tetsu Akiyama, Makoto Suematsu, Eishi Baba, Koichi Akashi, Hideyuki Saya, and Osamu Nagano

Précis: These findings establish a new functional role for EGFR in promoting the malignant potential of glioma cells by influencing amino acid transport at the cell surface.

2964 PDGF Engages an E2F-USP1 Signaling Pathway to Support ID2-Mediated Survival of Proneural Glioma Cells

Gilbert J. Rahme, Zhonghua Zhang, Alison L. Young, Chao Cheng, Eric J. Bivona, Steven N. Fiering, Yasuyuki Hitoshi, and Mark A. Israel

Précis: This study describes molecular events promoting proneural glioma formation downstream of PDGF signaling, with implications for potential therapeutic strategies for patients presenting with aberrant PDGF expression.

2977 Caspase-9b Interacts Directly with cIAP1 to Drive Agonist-Independent Activation of NF- κ B and Lung Tumorigenesis



Ngoc T. Vu, Margaret A. Park, Michael D. Shultz, Gamze B. Bulut, Amy C. Ladd, and Charles E. Chalfant

Précis: These findings identify a novel point for therapeutic intervention in NSCLC that may be tractable to small molecule inhibitors, with potentially broad applicability in this disease setting.

2990 Induction of Therapeutic Senescence in Vemurafenib-Resistant Melanoma by Extended Inhibition of CDK4/6

Akihiro Yoshida, Eric K. Lee, and J. Alan Diehl

Précis: These findings offer a mechanistic rationale for the use of the approved CDK4/6 inhibitor palbociclib in treating melanomas resistant to BRAF inhibition, with immediate implications for clinical translation.



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THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

3003 Enfortumab Vedotin Antibody–Drug Conjugate Targeting Nectin-4 Is a Highly Potent Therapeutic Agent in Multiple Preclinical Cancer Models



Pia M. Challita-Eid, Daulet Satpayev, Peng Yang, Zili An, Karen Morrison, Yuriy Shostak, Arthur Raitano, Rossana Nadell, Wendy Liu, Dawn Ratay Lortie, Linnette Capo, Alla Verlinsky, Monica Leavitt, Faisal Malik, Hector Aviña, Claudia I. Guevara, Nick Dinh, Sher Karki, Banmeet S. Anand, Daniel S. Pereira, Ingrid B.J. Joseph, Fernando Doñate, Kendall Morrison, and David R. Stover

Précis: These findings offer a preclinical proof of concept for an antibody drug conjugate that targets a cell adhesion molecule expressed by many solid tumors, providing a rationale for ongoing clinical trials.

3014 Intracrine VEGF Signaling Mediates the Activity of Prosurvival Pathways in Human Colorectal Cancer Cells

Rajat Bhattacharya, Xiang-Cang Ye, Rui Wang, Xia Ling, Madonna McManus, Fan Fan, Delphine Boulbes, and Lee M. Ellis

Précis: Therapeutically targeting intracellular VEGF signaling may enhance colon cancer cell killing, warranting further investigation of strategies that more completely block VEGF activity inside and outside of cells.

3025 p53 Loss in MYC-Driven Neuroblastoma Leads to Metabolic Adaptations Supporting Radioresistance



Orli Yogev, Karen Barker, Arti Sikka, Gilberto S. Almeida, Albert Hallsworth, Laura M. Smith, Yann Jamin, Ruth Ruddell, Alexander Koers, Hannah T. Webber, Florence I. Raynaud, Sergey Popov, Chris Jones, Kevin Petrie, Simon P. Robinson, Hector C. Keun, and Louis Chesler

Précis: Targeting oxidative stress pathways may represent a strategy to overcome the radioresistance associated with high-risk neuroblastomas exhibiting frequent loss of p53.

3036 FGFR1 Induces Glioblastoma Radioresistance through the PLC γ /Hif1 α Pathway

Valérie Gouazé-Andersson, Caroline Delmas, Marion Taurand, Judith Martinez-Gala, Solène Evrard, Sandrine Mazoyer, Christine Toulas, and Elizabeth Cohen-Jonathan-Moyal

Précis: These results offer a preclinical proof of concept that FGFR1 targeting can degrade radioresistance in glioblastoma, a widespread problem in this tumor, prompting clinical investigations of the use of FGFR1 inhibitors for radiosensitization.

3045 Extracellular Adenosine Production by ecto-5'-Nucleotidase (CD73) Enhances Radiation-Induced Lung Fibrosis

Florian Wirsdörfer, Simone de Leve, Federica Cappuccini, Therese Eldh, Alina V. Meyer, Eva Gau, Linda F. Thompson, Ning-Yuan Chen, Harry Karmouty-Quintana, Ute Fischer, Michael Kasper, Diana Klein, Jerry W. Ritchey, Michael R. Blackburn, Astrid M. Westendorf, Martin Stuschke, and Verena Jendrossek

Précis: These results offer a rationale for blocking the CD73/adenosine inflammatory pathway as a strategy to limit a serious side effect of thoracic irradiation in many patients, offering near-term clinical opportunities for this new application of CD73/adenosine blocking strategies.

3057 Human Helicase RECQL4 Drives Cisplatin Resistance in Gastric Cancer by Activating an AKT–YB1–MDR1 Signaling Pathway

Dongliang Mo, Hongbo Fang, Kaifeng Niu, Jing Liu, Meng Wu, Shiyu Li, Tienian Zhu, Mohammed A. Aleskandarany, Arvind Arora, Dileep N. Lobo, Srinivasan Madhusudan, Adayabalam S. Balajee, Zhenfen Chi, and Yongliang Zhao

Précis: These important results establish the DNA unwinding helicase RecQL4 as a critical mediator of cisplatin resistance in gastric cancer, providing a much needed new therapeutic rationale to improve treatment of this disease.

3067 Enhanced Histone Deacetylase Activity in Malignant Melanoma Provokes RAD51 and FANCD2-Triggered Drug Resistance

Andrea Krumm, Christina Barchhausen, Pelin Küçük, Karl-Heinz Tomaszowski, Carmen Loquai, Jörg Fahrner, Oliver Holger Krämer, Bernd Kaina, and Wynand Paul Roos

Précis: An important translational implication of this study is the prospect to deploy small molecule inhibitors of class I histone deacetylases to overcome drug resistance in melanoma.

3078 Polysome Profiling Links Translational Control to the Radioresponse of Glioblastoma Stem-like Cells


Amy Wahba, Barbara H. Rath, Kheem Bisht, Kevin Camphausen, and Philip J. Tofilon

Précis: Glioblastomas are generally treated with radiotherapy, and the characterization of polysomal RNAs generated in response to irradiation of glioblastoma stem-like cells in this study yields a new source of candidate drug targets in these cells to improve outcomes.

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TUMOR AND STEM CELL BIOLOGY

- 3088** NRF2 Intensifies Host Defense Systems to Prevent Lung Carcinogenesis, but After Tumor Initiation Accelerates Malignant Cell Growth
Hironori Satoh, Takashi Moriguchi, Daisuke Saigusa, Liam Baird, Lei Yu, Hirofumi Rokutan, Keiko Igarashi, Masahito Ebina, Tatsuhiro Shibata, and Masayuki Yamamoto
- Précis:* These findings suggest that resistance to lung cancer involves balance and timing in two opposing Nrf2-mediated events, including anticancer immunity and tumor growth.

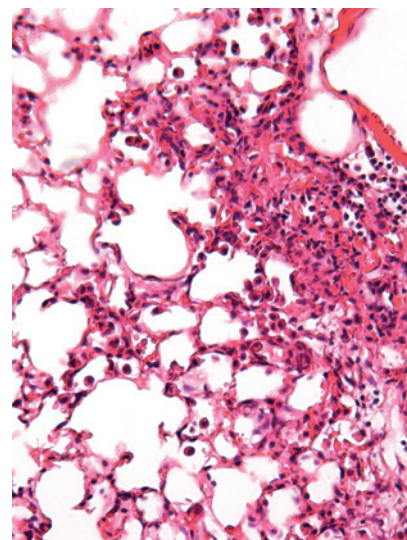
- 3097** Loss of Tet1-Associated 5-Hydroxymethylcytosine Is Concomitant with Aberrant Promoter Hypermethylation in Liver Cancer
 John P. Thomson, Raffaele Ottaviano, Elif B. Unterberger, Harri Lempiäinen, Arne Muller, Remi Terranova, Robert S. Illingworth, Shaun Webb, Alastair R.W. Kerr, Marcus J. Lyall, Amanda J. Drake, C. Roland Wolf, Jonathan G. Moggs, Michael Schwarz, and Richard R. Meehan
- Précis:* Tracking epigenetic patterns during liver carcinogenesis in the mouse suggests that aberrant DNA modifications precede histone modifications that enforce gene silencing events in cancer.

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ABOUT THE COVER

Radiation-induced pulmonary fibrosis constitutes a major adverse effect of thorax irradiation that develops 6 to 24 months after radiation therapy, with symptoms ranging from nonproductive cough and dyspnea to respiratory insufficiency in severe cases. A sophisticated network between resident cells, immune cells, and soluble mediators leads to the observed fibrotic alterations of the lung tissue. In a preclinical murine model, it was found that CD73-generated adenosine plays an active role in the pathogenesis of radiation-induced lung fibrosis driving excessive tissue remodeling. Targeting the CD73/adenosine axis reduced pathological fibrosis development, suggesting new routes for therapeutic intervention. For details, see article by Wirsdörfer and colleagues on page 3045.



LETTERS TO THE EDITOR

- 3109** Heterogeneity in Tumors and Resistance to EGFR TKI Therapy—Letter
Kenichi Suda, Christopher J. Rivard, Tetsuya Mitsudomi, and Fred R. Hirsch
- 3111** Heterogeneity in Tumors and Resistance to EGFR TKI Therapy—Response
Takeshi Shimamura

Cancer Research

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

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