

BREAKING ADVANCES

- 241** Highlights from Recent Cancer Literature

OBITUARY

- 243** Emmanuel Farber: In Memoriam (1918–2014)
Ezio Laconi, Richard G. Hegele, Michael W. Lieberman,
Rajalakshmi Srinivasan, and Sarma S.R. Dittakavi

REVIEWS

- 245** Colorectal Cancer Heterogeneity and Targeted Therapy: A Case for Molecular Disease Subtypes
Janneke F. Linnekamp, Xin Wang, Jan Paul Medema, and Louis Vermeulen
- 250** Targeting the eIF4F Translation Initiation Complex: A Critical Nexus for Cancer Development
Jerry Pelletier, Jeremy Graff, Davide Ruggero, and Nahum Sonenberg

PRIORITY REPORTS

- 264** Whole-Exome Sequencing Reveals Frequent Genetic Alterations in *BAP1*, *NF2*, *CDKN2A*, and *CUL1* in Malignant Pleural Mesothelioma
Guangwu Guo, Juliann Chmielecki, Chandra Goparaju, Adriana Heguy, Igor Dolgalev, Michele Carbone, Sara Seepo, Matthew Meyerson, and Harvey I. Pass
Précis: This is the first unbiased view of the molecular basis of mesothelioma, revealing frequent genetic alterations that will offer a valuable foundation for biologic studies.
- 270** Breast Cancer Risk in Metabolically Healthy but Overweight Postmenopausal Women
Marc J. Gunter, Xianhong Xie, Xiaonan Xue, Geoffrey C. Kabat, Thomas E. Rohan, Sylvia Wassertheil-Smoller, Gloria Y.F. Ho, Judith Wylie-Rosett, Theresa Greco, Herbert Yu, Jeannette Beasley, and Howard D. Strickler
Précis: These provocative results demonstrate that metabolic health as defined by insulin resistance may be more relevant for breast cancer risk than obesity per se.

MICROENVIRONMENT AND IMMUNOLOGY

- 275** L-Arginine Depletion Blunts Antitumor T-cell Responses by Inducing Myeloid-Derived Suppressor Cells
Matthew Fletcher, Maria E. Ramirez, Rosa A. Sierra, Patrick Raber, Paul Thevenot, Amir A. Al-Khami, Dulfary Sanchez-Pino, Claudia Hernandez, Dorota D. Wyczzechowska, Augusto C. Ochoa, and Paulo C. Rodriguez
Précis: These results suggest the need for caution in clinical development of pegylated forms of the arginine catabolizing enzyme Arginase I as a cancer therapy based on its ability to promote accumulation of myeloid-derived suppressor cells that harm antitumor immune responses and potentially worsen clinical outcomes.
- 284** Snail1-Expressing Fibroblasts in the Tumor Microenvironment Display Mechanical Properties That Support Metastasis
Jelena Stanisavljevic, Jordina Loubat-Casanovas, Mercedes Herrera, Tomás Luque, Raúl Peña, Ana Lluch, Joan Albanell, Félix Bonilla, Ana Rovira, Cristina Peña, Daniel Navajas, Federico Rojo, Antonio García de Herreros, and Josep Baulida
Précis: Cancer-associated fibroblasts that express the EMT regulator Snail contribute to the reorganization of the tumor microenvironment in a way that promotes the invasive behavior of tumor cells.
- 296** Akt Inhibition Enhances Expansion of Potent Tumor-Specific Lymphocytes with Memory Cell Characteristics
Joseph G. Crompton, Madhusudhanan Sukumar, Rahul Roychoudhuri, David Clever, Alena Gros, Robert L. Eil, Eric Tran, Ken-ichi Hanada, Zhiya Yu, Douglas C. Palmer, Sid P. Kerkar, Ryan D. Michalek, Trevor Upham, Anthony Leonardi, Nicolas Acquavella, Ena Wang, Francesco M. Marincola, Luca Gattinoni, Pawel Muranski, Mark S. Sundrud, Christopher A. Klebanoff, Steven A. Rosenberg, Douglas T. Fearon, and Nicholas P. Restifo
Précis: Like other oncoprotein-targeting drugs initially conceptualized simply as tools to kill tumor cells, Akt inhibitors can be shown to act as immunomodulators that markedly enhance the properties of antitumor T cells, possibly a more broadly useful therapeutic aspect.

Table of Contents

306 Novel Mechanism of Macrophage-Mediated Metastasis Revealed in a Zebrafish Model of Tumor Development

Jian Wang, Ziquan Cao, Xing-Mei Zhang, Masaki Nakamura, Meili Sun, Johan Hartman, Robert A. Harris, Yuping Sun, and Yihai Cao

Précis: This study used a novel zebrafish model of cancer metastasis to implicate tumor-associated macrophages in the initial early step of intravasation, the first stage of metastasis that is difficult to study at the earliest times of tumor development.

MOLECULAR AND CELLULAR PATHOBIOLOGY

316 Hypoxia-Induced SUMOylation of E3 Ligase HAF Determines Specific Activation of HIF2 in Clear-Cell Renal Cell Carcinoma

Mei Yee Koh, Vuvi Nguyen, Robert Lemos Jr, Bryant G. Darnay, Galina Kiriakova, Mena Abdelmelek, Thai H. Ho, Jose Karam, Federico A. Monzon, Eric Jonasch, and Garth Powis

Précis: These findings show how a novel E3 ligase controls the oncogenic function of HIF2, a less-studied relative of the hypoxia controlled transcription factor HIF1 that has a distinct function in the development of aggressive kidney cancers.

330 Distinct Functions of Epidermal and Myeloid-Derived VEGF-A in Skin Tumorigenesis Mediated by HPV8

Xiaolei Ding, Tina Lucas, Gian P. Marcuzzi, Herbert Pfister, and Sabine A. Eming

Précis: These findings offer new mechanistic insights into distinct functions of VEGF-A expressed by different cell types in virally induced skin cancers, with possible implications for preventing this disease.

344 KAP1 Promotes Proliferation and Metastatic Progression of Breast Cancer Cells

Joseph B. Addison, Colton Koontz, James H. Fugett, Chad J. Creighton, Dongquan Chen, Mark K. Farrugia, Renata R. Padon, Maria A. Voronkova, Sarah L. McLaughlin, Ryan H. Livengood, Chen-Chung Lin, J. Michael Ruppert, Elena N. Pugacheva, and Alexey V. Ivanov

Précis: These findings elucidate the role of an important developmental transcription network in promoting breast cancer growth and metastasis, with potential implications for a broad-based approach to treat advanced breast cancers.

356 Agr2 Mediates Paracrine Effects on Stromal Fibroblasts That Promote Invasion by Gastric Signet-Ring Carcinoma Cells

Tadahiro Tsuji, Rika Satoyoshi, Namiko Aiba, Takanori Kubo, Kazuyoshi Yanagihara, Daichi Maeda, Akiteru Goto, Kazuo Ishikawa, Masakazu Yashiro, and Masamitsu Tanaka

Précis: These findings highlight a disulfide isomerase that is normally intracellular but secreted by a class of gastric cancers, where it coordinates invasive cell behaviors in the tumor microenvironment and may present a tractable therapeutic target.

367 miR30a Inhibits LOX Expression and Anaplastic Thyroid Cancer Progression

Myriem Boufraqueh, Naris Nilubol, Lisa Zhang, Sudheer Kumar Gara, Samira M. Sadowski, Amit Mehta, Mei He, Sean Davis, Jennifer Dreiling, John A. Copland, Robert C. Smallridge, Martha M. Quezado, and Electron Kebebew

Précis: Thyroid cancer is typically readily treatable, but the anaplastic form, which is highly aggressive and associated with higher mortality, is a focus of this study identifying the targetable enzyme lysyl oxidase as a critical oncogenic driver.

378 TUSC4 Functions as a Tumor Suppressor by Regulating BRCA1 Stability

Yang Peng, Hui Dai, Edward Wang, Curtis Chun-Jen Lin, Wei Mo, Guang Peng, and Shiao-Yih Lin

Précis: These results provide a set of genetic and biologic proofs that the candidate tumor suppressor gene TUSC4 functions as a bona fide suppressor by regulating the protein stability and function of BRCA1 in breast cancer.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

387 In Vivo Radioimaging of Bradykinin Receptor B1, a Widely Overexpressed Molecule in Human Cancer

Kuo-Shyan Lin, Jinhe Pan, Guillaume Amouroux, Gulisa Turashvili, Felix Mesak, Navjit Hundal-Jabal, Maral Pourghiasian, Joseph Lau, Silvia Jenni, Samuel Aparicio, and François Bénard

Précis: These results offer preclinical proof of concept for noninvasive imaging of a peptide receptor that is widely overexpressed in many human cancers as a generalized tool for monitoring tumor masses in patients.



Table of Contents

394 A Urokinase Receptor–Bim Signaling Axis Emerges during EGFR Inhibitor Resistance in Mutant EGFR Glioblastoma

Jill Wykosky, Jingjing Hu, German G. Gomez, Tiffany Taylor, Genaro R. Villa, Donald Pizzo, Scott R. Vandenberg, Amy Haseley Thorne, Clark C. Chen, Paul S. Mischel, Steven L. Goniias, Webster K. Cavenee, and Frank B. Furnari

Précis: These studies reveal a type of therapeutic resistance in EGFR mutant forms of aggressive brain tumors, in which expression of the proapoptotic protein BIM could determine outcomes with anti-EGFR therapy.

405 Kinome-wide Functional Screen Identifies Role of PLK1 in Hormone-Independent, ER-Positive Breast Cancer

Neil E. Bholra, Valerie M. Jansen, Sangeeta Bafna, Jennifer M. Giltneane, Justin M. Balko, Mónica V. Estrada, Ingrid Meszoely, Ingrid Mayer, Vandana Abramson, Fei Ye, Melinda Sanders, Teresa C. Dugger, Eliezer V. Allen, and Carlos L. Arteaga

Précis: These findings suggest that breast cancers that recur in a hormone-independent form may be sensitive to attack by experimental small molecule inhibitors that target the mitotic kinase PLK1, the most advanced of which is currently in phase III trials for acute myeloid leukemias.

415 TUBB3/ β III-Tubulin Acts through the PTEN/AKT Signaling Axis to Promote Tumorigenesis and Anoikis Resistance in Non–Small Cell Lung Cancer

Joshua A. McCarroll, Pei Pei Gan, Rafael B. Erlich, Marjorie Liu, Tanya Dwarthe, Sharon S. Sagnella, Mia C. Akerfeldt, Lu Yang, Amelia L. Parker, Melissa H. Chang, Michael S. Shum, Frances L. Byrne, and Maria Kavallaris

Précis: These findings reveal how a structural protein tightly associated with aggressive disease and therapeutic resistance in lung adenocarcinomas and other cancers influences tumor growth.

TUMOR AND STEM CELL BIOLOGY

426 Activin Upregulation by NF- κ B Is Required to Maintain Mesenchymal Features of Cancer Stem–like Cells in Non–Small Cell Lung Cancer

J. Jacob Wamsley, Manish Kumar, David F. Allison, Sheena H. Clift, Caitlyn M. Holzknrecht, Szymon J. Szymura, Stephen A. Hoang, Xiaojiang Xu, Christopher A. Moskaluk, David R. Jones, Stefan Bekiranov, and Marty W. Mayo

Précis: These findings point to a readily targeted extracellular factor needed to maintain the stem-like characteristics of tumor-initiating cells in non–small cell lung cancers, with potential therapeutic implications.

436 Loss of Estrogen-Regulated microRNA Expression Increases HER2 Signaling and Is Prognostic of Poor Outcome in Luminal Breast Cancer



Shannon T. Bailey, Thomas Westerling, and Myles Brown

Précis: An miRNA cluster that regulates HER2 levels in ER⁺ luminal A breast cancers may offer a simple biomarker of poor treatment outcomes in this disease setting.

446 PI3K/mTOR Dual Inhibitor VS-5584 Preferentially Targets Cancer Stem Cells



Vihren N. Kolev, Quentin G. Wright, Christian M. Vidal, Jennifer E. Ring, Irina M. Shapiro, Jill Ricono, David T. Weaver, Mahesh V. Padval, Jonathan A. Pachter, and Qunli Xu

Précis: A dual specificity small molecule inhibitor may provide a means to leverage the efficacy of cytotoxic chemotherapy and achieve more durable remissions in patients.

456 Nitric Oxide Mediates Metabolic Coupling of Omentum-Derived Adipose Stroma to Ovarian and Endometrial Cancer Cells

Bahar Salimian Rizi, Christine Caneba, Aleksandra Nowicka, Ahmad W. Nabiyyar, Xinran Liu, Kevin Chen, Ann Klopp, and Deepak Nagrath

Précis: Blocking both secreted arginine levels and nitric oxide synthesis may yield a therapeutic benefit in ovarian and endometrial tumors by withdrawing a critical stromal support provided by adipose tissue in these settings.

CORRECTION

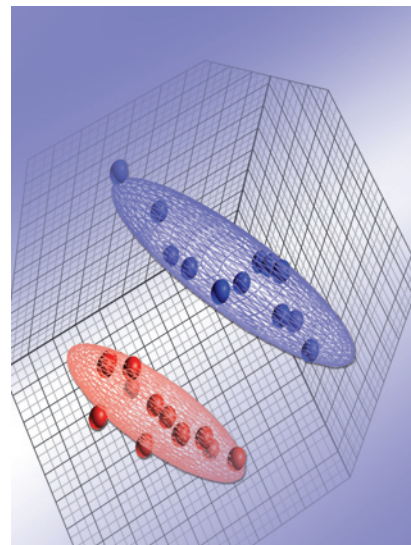
472 Correction: Tid1-L Inhibits EGFR Signaling in Lung Adenocarcinoma by Enhancing EGFR Ubiquitinylation and Degradation

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Table of Contents

ABOUT THE COVER

Some drugs initially aimed at deranged oncogenic pathways in tumors are finding more reliable targets in T cells as modulators of their cancer-killing activity. An Akt inhibitor was found to have a profound impact on gene transcription, metabolic fitness, long-lived persistence, and function of tumor-specific CD8⁺ T cells. This graphic shows a principal component analysis of changes in global gene transcription caused by inhibition of Akt in T cells. For details, see the article by Crompton and colleagues on page 296.



Cancer Research

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

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