

## CANCER RESEARCH

## TABLE OF CONTENTS

## BREAKING INSIGHTS

- 515 **Highlights from Recent Cancer Literature**

## REVIEWS

- 517 **Translational Regulation of Cancer Metastasis**  
Douglas S. Micalizzi, Richard Y. Ebright, Daniel A. Haber, and Shyamala Maheswaran
- 525 **Histone Methyltransferase SETDB1: A Common Denominator of Tumorigenesis with Therapeutic Potential**  
Dimitrios Strepkos, Mariam Markouli, Alexia Klonou, Athanasios G. Papavassiliou, and Christina Piperi

## CANCER RESEARCH HIGHLIGHTS

- 535 **SCIRT lncRNA Blocks the Shot of Breast Cancer Cells Self-Renewal Mechanism**  
Barbara Pardini and Mihnea P. Dragomir  
See related article, p. 580
- 537 **The *ESR1* Mutations: From Bedside to Bench to Bedside**  
Francisco Hermida-Prado and Rinath Jeselsohn  
See related article, p. 539

## GENOME AND EPIGENOME

- 539 **Estrogen Receptor Alpha Mutations in Breast Cancer Cells Cause Gene Expression Changes through Constant Activity and Secondary Effects**  
Spencer Arnesen, Zannel Blanchard, Michelle M. Williams, Kristofer C. Berrett, Zheqi Li, Steffi Oesterreich, Jennifer K. Richer, and Jason Gertz  
This study demonstrates the multiple roles of mutant ER in breast cancer progression, including constant ER activity and secondary regulatory effects on gene expression and chromatin accessibility.  
See related commentary, p. 537  
See related article by Williams and colleagues, p. 732

## METABOLISM AND CHEMICAL BIOLOGY

- 552 **Dysregulated Glutamate Transporter SLC1A1 Propels Cystine Uptake via  $Xc^-$  for Glutathione Synthesis in Lung Cancer**  
**A C** Wenzheng Guo, Kaimi Li, Beibei Sun, Dongliang Xu, Lingfeng Tong, Huijing Yin, Yueling Liao, Hongyong Song, Tong Wang, Bo Jing, Min Hu, Shuli Liu, Yanbin Kuang, Jing Ling, Qi Li, Yadi Wu, Qi Wang, Feng Yao, Binhua P. Zhou, Shu-Hai Lin, and Jiong Deng  
Cellular GSH in cancer cells is not only determined by upregulated  $Xc^-$  but also by dysregulated glutamate transporters, which provide additional targets for therapeutic intervention.
- 567 **Altered Mitochondria Functionality Defines a Metastatic Cell State in Lung Cancer and Creates an Exploitable Vulnerability**  
Chen-Hua Chuang, Madeleine Dorsch, Philip Dujardin, Sukrit Silas, Kristina Ueffing, Johanna M. Hölken, Dian Yang, Monte M. Winslow, and Barbara M. Grüner  
This study characterizes altered mitochondria functionality of the metastatic cell state in lung cancer and opens new avenues for metastasis-specific therapeutic targeting.

## MOLECULAR CELL BIOLOGY

- 580 **SCIRT lncRNA Restrains Tumorigenesis by Opposing Transcriptional Programs of Tumor-Initiating Cells**  
Sladjana Zagorac, Alex de Giorgio, Aleksandra Dabrowska, Mark Kalisz, Nuria Casas-Vila, Paul Cathcart, Angela Yiu, Silvia Ottaviani, Neta Degani, Ylenia Lombardo, Alistair Tweedie, Tracy Nissan, Keith W. Vance, Igor Ulitsky, Justin Stebbing, and Leandro Castellano  
These findings show that a novel lncRNA SCIRT counteracts breast tumorigenesis by opposing transcriptional networks associated with cell cycle and self-renewal.  
See related commentary, p. 535

# TABLE OF CONTENTS

## TUMOR BIOLOGY AND IMMUNOLOGY

- 594** **Gain of HIF1 Activity and Loss of miRNA *let-7d* Promote Breast Cancer Metastasis to the Brain via the PDGF/PDGFR Axis**  
Christof B. Wyss, Nathalie Duffey, Sanam Peyvandi, David Barras, Amaia Martinez Usatorre, Oriana Coquoz, Pedro Romero, Mauro Delorenzi, Girieca Lorusso, and Curzio Rüegg  
These findings show that loss of miRNA *let-7d* and active HIF1 signaling promotes breast cancer brain metastasis via PDGF and that pharmacologic inhibition of PDGFR suppresses brain metastasis, suggesting novel therapeutic opportunities.  
**See related article by Thies and colleagues, p. 606**
- 606** **Stromal Platelet-Derived Growth Factor Receptor- $\beta$  Signaling Promotes Breast Cancer Metastasis in the Brain**  
Katie A. Thies, Anisha M. Hammer, Blake E. Hildreth III, Sarah A. Steck, Jonathan M. Spehar, Raleigh D. Kladney, Jennifer A. Geisler, Manjusri Das, Luke O. Russell, Jerome F. Bey IV, Chelsea M. Bolyard, Robert Pilarski, Anthony J. Trimboli, Maria C. Cuitiño, Christopher S. Koivisto, Daniel G. Stover, Lynn Schoenfield, Jose Otero, Jonathan P. Godbout, Arnab Chakravarti, Matthew D. Ringel, Bhuvanewari Ramaswamy, Zaibo Li, Balveen Kaur, Gustavo Leone, Michael C. Ostrowski, Steven T. Sizemore, and Gina M. Sizemore  
This study reveal a previously unknown role for PDGFB-to-PDGFR $\beta$  paracrine signaling in the promotion of breast cancer brain metastases and support the prognostic and therapeutic clinical utility of this pathway for patients.  
**See related article by Wyss and colleagues, p. 594**
- 619** **A High-Content Screen Identifies Drugs That Restrict Tumor Cell Extravasation across the Endothelial Barrier**  
Georg Hilfenhaus, Ana Mompeón, Jonathan Freshman, Divya P. Prajapati, Gloria Hernandez, Vanessa M. Freitas, Feiyang Ma, Adam D. Langenbacher, Snezana Mirkov, Dana Song, Byoung-Kyu Cho, Young Ah Goo, Matteo Pellegrini, Jau-Nian Chen, Robert Damoiseaux, and M. Luisa Iruela-Arispe  
A high-content screen identified niclosamide as an effective drug that restricts tumor cell extravasation by enhancing endothelial barrier stability through modulation of molecular signaling, chemokines, and tumor-endothelial cell interactions.
- 634** **Myeloma-Modified Adipocytes Exhibit Metabolic Dysfunction and a Senescence-Associated Secretory Phenotype**  
Heather Fairfield, Amel Dudakovic, Casper M. Khatib, Mariah Farrell, Samantha Costa, Carolyne Falank, Maja Hinge, Connor S. Murphy, Victoria DeMambro, Jessica A. Pettitt, Christine W. Lary, Heather E. Driscoll, Michelle M. McDonald, Moustapha Kassem, Clifford Rosen, Thomas L. Andersen, Andre J. van Wijnen, Abbas Jafari, and Michaela R. Reagan  
This study changes the foundational understanding of how cancer cells hijack the bone marrow microenvironment and demonstrates that tumor cells induce senescence and metabolic changes in adipocytes, potentially driving new therapeutic directions.
- 648** **Hyal2 Expression in Tumor-Associated Myeloid Cells Mediates Cancer-Related Inflammation in Bladder Cancer**  
Paul R. Dominguez-Gutierrez, Elizabeth P. Kwenda, William Donelan, Pdraic O'Malley, Paul L. Crispin, and Sergei Kusmartsev  
This study identifies Hyal2-expressing tumor-associated myeloid cells of monocyte-macrophage lineage as contributors to hyaluronan degradation in bladder cancer tissue, leading to accumulation of inflammatory and proangiogenic low molecular weight hyaluronan fragments.
- 658** **Myeloid-Derived Suppressor Cells Are a Major Source of Wnt5A in the Melanoma Microenvironment and Depend on Wnt5A for Full Suppressive Activity**  
Stephen M. Douglass, Mitchell E. Fane, Emilio Sanseviero, Brett L. Ecker, Curtis H. Kugel III, Reeti Behera, Vinit Kumar, Evgenii N. Tcyganov, Xiangfan Yin, Qin Liu, Yash Chhabra, Gretchen M. Alicea, Rejji Kuruvilla, Dmitry I. Gabrilovich, and Ashani T. Weeraratna  
These findings demonstrate that myeloid cells provide a major source of Wnt5A to facilitate metastatic potential in melanoma cells and rely on Wnt5A for their immunosuppressive function.
- 671** **Folate Receptor Beta Designates Immunosuppressive Tumor-Associated Myeloid Cells That Can Be Reprogrammed with Folate-Targeted Drugs**  
Gregory M. Cresswell, Bingbing Wang, Erin M. Kischuk, Meaghan M. Broman, Rami A. Alfar, Renee E. Vickman, Dimiter S. Dimitrov, Sumith A. Kularatne, Chandru P. Sundaram, Sunil Singhal, Evgeniy B. Eruslanov, Scott A. Crist, Bennett D. Elzey, Timothy L. Ratliff, and Philip S. Low  
FR $\beta$  serves as both a means to identify and target MDSCs and TAMs within the tumor, allowing for delivery of immunomodulatory compounds to tumor myeloid cells in a variety of cancers.

# TABLE OF CONTENTS

- 685** **Cyclophosphamide and Vinorelbine Activate Stem-Like CD8<sup>+</sup> T Cells and Improve Anti-PD-1 Efficacy in Triple-Negative Breast Cancer**  
**AC** Paolo Falvo, Stefania Orecchioni, Roman Hillje, Alessandro Raveane, Patrizia Mancuso, Chiara Camisaschi, Lucilla Luzi, PierGiuseppe Pelicci, and Francesco Bertolini  
A combinatorial therapy in mouse models of breast cancer increases checkpoint inhibition by activating antigen-presenting cells, enhancing intratumoral Tcf1<sup>+</sup> stem-like CD8<sup>+</sup> T cells, and increasing progenitor exhausted CD8<sup>+</sup> T cells.
- 698** **Axl and Mertk Receptors Cooperate to Promote Breast Cancer Progression by Combined Oncogenic Signaling and Evasion of Host Antitumor Immunity**  
Viralkumar Davra, Sushil Kumar, Ke Geng, David Calianese, Dhriti Mehta, Varsha Gadiyar, Canan Kasikara, Kevin C. Lahey, Yun-juan Chang, Michael Wichroski, Chan Gao, Mariana S. De Lorenzo, Sergei V. Kotenko, Tessa Bergsbaken, Pankaj K. Mishra, William C. Gause, Michael Quigley, Thomas E. Spires, and Raymond B. Birge  
This study demonstrates how TAM receptors act both as oncogenic tyrosine kinases and as receptors that mediate immune evasion in cancer progression.
- 724** **Radiomic Detection of EGFR Mutations in NSCLC**  
Giovanni Rossi, Emanuele Barabino, Alessandro Fedeli, Gianluca Ficarra, Simona Coco, Alessandro Russo, Vincenzo Adamo, Francesco Buemi, Lodovica Zullo, Mariella Dono, Giuseppa De Luca, Luca Longo, Maria Giovanna Dal Bello, Marco Tagliamento, Angela Alama, Giuseppe Cittadini, Paolo Pronzato, and Carlo Genova  
These findings demonstrate that data normalization and "test-retest" methods might improve the performance of machine learning models on radiomics images and increase their reliability when used on external validation datasets.
- 732** **Steroid Hormone Receptor and Infiltrating Immune Cell Status Reveals Therapeutic Vulnerabilities of *ESR1*-Mutant Breast Cancer**  
Michelle M. Williams, Nicole S. Spoelstra, Spencer Arnesen, Kathleen I. O'Neill, Jessica L. Christenson, Jordan Reese, Kathleen C. Torkko, Andrew Goodspeed, Emmanuel Rosas, Toru Hanamura, Sharon B. Sams, Zheqi Li, Steffi Oesterreich, Rebecca B. Riggins, Britta M. Jacobsen, Anthony Elias, Jason Gertz, and Jennifer K. Richer  
Targetable alterations in MBC, including AR, CH3L1, and ISG, arise following estrogen-deprivation, and ER-mutant metastases may respond to immunotherapies due to elevated PD-L1<sup>+</sup> macrophages.  
See related article by Arnesen and colleagues, p. 539
- 747** **Activation of Receptor Tyrosine Kinases Mediates Acquired Resistance to MEK Inhibition in Malignant Peripheral Nerve Sheath Tumors**  
Jiawan Wang, Kai Pollard, Ana Calizo, and Christine A. Pratilas  
This study demonstrates that MEKi plus MET inhibitor may delay or prevent a novel mechanism of acquired MEKi resistance, with clinical implications for MPNST patients harboring *NF1* alterations.
- 763** **Optimized Doxorubicin Chemotherapy for Diffuse Large B-cell Lymphoma Exploits Nanocarrier Delivery to Transferrin Receptors**  
Artavazd Arumov, Piumi Y. Liyanage, Asaad Trabolsi, Evan R. Roberts, Lingxiao Li, Bráulio C.L.B. Ferreira, Zhen Gao, Yuguang Ban, Austin D. Newsam, Melissa W. Taggart, Francisco Vega, Daniel Bilbao, Roger M. Leblanc, and Jonathan H. Schatz  
Targeted nanoparticle delivery of doxorubicin chemotherapy via the TRF1 receptor presents a new opportunity against high-risk DLBCL tumors using potency and precision.

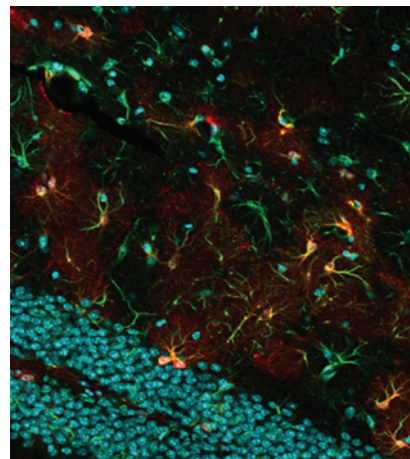
## TRANSLATIONAL SCIENCE

**AC** AC icon indicates Author Choice  
For more information please visit [www.aacrjournals.org](http://www.aacrjournals.org)

# TABLE OF CONTENTS

## ABOUT THE COVER

Stromal specific activation of platelet-derived growth factor receptor- $\beta$  (PDGFR $\beta$ ) in the metastatic microenvironment promotes breast cancer metastasis to the brain. Specifically, the *Fsp1-cre* transgene was used to hyperactivate PDGFR $\beta$  in the mesenchymal population. A confocal image shows native tdTomato fluorescence (red) and GFAP (green) immunostaining in the brain stroma of a *Fsp1-cre;Rosa26-LSL-tdTomato* reporter mouse. The dual tdTomato(FSP1)/GFAP-positive cells represent a novel stromal population implicated in creating a prometastatic niche through PDGFR $\beta$  signaling. For details, see article by Thies and colleagues on page 606.



# Cancer Research

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

81 (3)

*Cancer Res* 2021;81:515-775.

**Updated version** Access the most recent version of this article at:  
<http://cancerres.aacrjournals.org/content/81/3>

**E-mail alerts** [Sign up to receive free email-alerts](#) related to this article or journal.

**Reprints and Subscriptions** To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at [pubs@aacr.org](mailto:pubs@aacr.org).

**Permissions** To request permission to re-use all or part of this article, use this link <http://cancerres.aacrjournals.org/content/81/3>. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.