

BREAKING ADVANCES

- 3439** Highlights from Recent Cancer Literature


CANCER RESEARCH 75th ANNIVERSARY COMMENTARIES

- 3441** Commentary on "Tumor Heterogeneity and the Biology of Cancer Invasion and Metastasis"
Isaiah J. Fidler
- 3443** Short-Term Screening Assays for the Identification of Therapeutics for Cancer
Deborah E. Citrin

REVIEW

- 3446** DNA Methylation in Cancer and Aging
Michael Klutstein, Deborah Nejman, Razi Greenfield, and Howard Cedar

INTEGRATED SYSTEMS AND TECHNOLOGIES


- 3451** Label-Free Neurosurgical Pathology with Stimulated Raman Imaging
Fa-Ke Lu, David Calligaris, Olutayo I. Olubiyi, Isaiah Norton, Wenlong Yang, Sandro Santagata, X. Sunney Xie, Alexandra J. Golby, and Nathalie Y.R. Agar
Précis: This study establishes a new methodology and provides a new reference system for label-free neurosurgical pathology to help improve guidance for brain tumor surgery.
- 3463** Identification of MYC-Dependent Transcriptional Programs in Oncogene-Addicted Liver Tumors
 Theresia R. Kress, Paola Pellanda, Luca Pellegrinet, Valerio Bianchi, Paola Nicoli, Mirko Doni, Camilla Recordati, Salvatore Bianchi, Luca Rotta, Thelma Capra, Micol Ravà, Alessandro Verrecchia, Enrico Radaelli, Trevor D. Littlewood, Gerard I. Evan, and Bruno Amati
Précis: Mapping Myc-dependent gene expression programs underlying liver tumor growth and maintenance reveals the primary regulatory events associated with oncogene addiction, thus providing a comprehensive source of potential therapeutic targets that are likely to be indispensable for tumor maintenance.

MICROENVIRONMENT AND IMMUNOLOGY

- 3473** Adoptive Transfer of CD8⁺ T Cells Generated from Induced Pluripotent Stem Cells Triggers Regressions of Large Tumors Along with Immunological Memory
Hidehito Saito, Keisuke Okita, Alfred E. Chang, and Fumito Ito
Précis: This important study shows how an unlimited number of phenotypically defined, functional, and expandable antigen-specific T cells can be generated for cancer immunotherapy from pluripotent stem cells, with important implications for adoptive T-cell-based treatment modalities.
- 3484** Antagonizing Integrin $\beta 3$ Increases Immunosuppression in Cancer
Xinming Su, Alison K. Esser, Sarah R. Amend, Jingyu Xiang, Yalin Xu, Michael H. Ross, Gregory C. Fox, Takayuki Kobayashi, Veronica Steri, Kirsten Roomp, Francesca Fontana, Michelle A. Hurchla, Brett L. Knolhoff, Melissa A. Meyer, Elizabeth A. Morgan, Julia C. Tomasson, Joshua S. Novack, Wei Zou, Roberta Faccio, Deborah V. Novack, Stephen D. Robinson, Steven L. Teitelbaum, David G. DeNardo, Jochen G. Schneider, and Katherine N. Weilbaecher
Précis: Integrin $\beta 3$ activation regulates the balance between antitumor and protumor immune cells through effects on STAT6/STAT1 signaling, probably explaining the generally poor efficacy of integrin antagonists in the clinic and raising questions about their cancer therapeutic utility.
- 3496** T-cell Landscape in a Primary Melanoma Predicts the Survival of Patients with Metastatic Disease after Their Treatment with Dendritic Cell Vaccines
Angela Vasaturo, Altuna Halilovic, Kalijn F. Bol, Dagmar I. Verweij, Willeke A.M. Blokk, Cornelis J.A. Punt, Patricia J.T.A. Groenen, J. Han J.M. van Krieken, Johannes Textor, I. Jolanda M. de Vries, and Carl G. Figdor
Précis: These findings suggest what appears to be a highly accurate biomarker for predicting the survival outcome of melanoma patients treated by administration with a dendritic cell vaccine.

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MOLECULAR AND CELLULAR PATHOBIOLOGY

- 3507** **YAP Mediates Tumorigenesis in Neurofibromatosis Type 2 by Promoting Cell Survival and Proliferation through a COX-2–EGFR Signaling Axis**
William Guerrant, Smitha Kota, Scott Troutman, Vinay Mandati, Mohammad Fallahi, Anat Stemmer-Rachamimov, and Joseph L. Kissil
Précis: This study illuminates the molecular pathogenesis of neurofibromatosis type 2, with possible implications for its treatment with inhibitors of prostaglandin metabolism that could clinically benefit patients.
- 3520** **MYC Is a Crucial Mediator of TGFβ-Induced Invasion in Basal Breast Cancer**
 Magdalena A. Cichon, Megan E. Moruzzi, Tiziana A. Shqau, Erin Miller, Christine Mehner, Stephen P. Ethier, John A. Copland, Evette S. Radisky, and Derek C. Radisky
Précis: These findings show that inhibiting MYC can drive cell invasion and metastasis of basal breast cancer cells by activating a TGFβ signaling loop that involves integrin-αvβ3 and that can be blocked by inhibiting SRC.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

- 3531** **Lenalidomide Stabilizes the Erythropoietin Receptor by Inhibiting the E3 Ubiquitin Ligase RNF41**
Ashley A. Basiorka, Kathy L. McGraw, Leentje De Ceuninck, Lori N. Griner, Ling Zhang, Justine A. Clark, Gisela Caceres, Lubomir Sokol, Rami S. Komroki, Gary W. Reuther, Sheng Wei, Jan Tavernier, and Alan F. List
Précis: These findings illuminate a new mechanism of action for a thalidomide-related drug used clinically to treat multiple myeloma and to inhibit angiogenesis, offering an explanation for how this drug also augments responsiveness to a biologic that increases red blood cell production.
- 3541** **LIM Kinase Inhibitor Pyr1 Reduces the Growth and Metastatic Load of Breast Cancers**
Chloé Prunier, Véronique Josserand, Julien Vollaire, Evelyne Beerling, Christos Petropoulos, Olivier Destaing, Christopher Montemagno, Amandine Hurbin, Renaud Prudent, Leanne de Koning, Reuben Kapur, Pascale A. Cohen, Corinne Albiges-Rizo, Jean-Luc Coll, Jacco van Rheenen, Marc Billaud, and Laurence Lafanechère
Précis: These results provide a preclinical proof of concept concerning how a small-molecule inhibitor of LIMK kinases may offer a strategy to treat taxane-resistant breast tumors and metastases.


- 3553** **Cell Cycle–Dependent Mechanisms Underlie Vincristine-Induced Death of Primary Acute Lymphoblastic Leukemia Cells**
Anisha Kothari, Walter N. Hittelman, and Timothy C. Chambers
Précis: These findings show how the microtubule targeting cancer drug vincristine induces cell death in multiple ways, depending on cell cycle status, illuminating the basis for the anticancer effects of this type of widely employed chemotherapy.
- 3562** **miR-339-3p Is a Tumor Suppressor in Melanoma**
 Claudia E.M. Weber, Chonglin Luo, Agnes Hotz-Wagenblatt, Adriane Gardyan, Theresa Kordaß, Tim Holland-Letz, Wolfram Osen, and Stefan B. Eichmüller
Précis: These findings identify and preclinically validate a microRNA that targets the BCL2-related protein MCL1, which has a specific function in cancer cell invasion distinct from its role in cell survival.
- 3572** **mda-7/IL-24 Induces Cell Death in Neuroblastoma through a Novel Mechanism Involving AIF and ATM**
Praveen Bhoopathi, Nathaniel Lee, Anjan K. Pradhan, Xue-Ning Shen, Swadesh K. Das, Devanand Sarkar, Luni Emdad, and Paul B. Fisher
Précis: A cytokine known to have cancer-fighting activity is rationalized here for potential applications in the treatment of neuroblastoma, a common and often deadly pediatric tumor.
- 3583** **Noninvasive In Vivo Imaging and Biologic Characterization of Thyroid Tumors by ImmunoPET Targeting of Galectin-3**
Calogero D'Alessandria, Sten Braesch-Andersen, Kristel Bejo, Sybille Reder, Birgit Blechert, Markus Schwaiger, and Armando Bartolazzi
Précis: These findings provide a method to improve the clinical management of patients with thyroid nodules, while reducing unnecessary surgery and social costs.
- 3593** **The Small Molecule IMR-1 Inhibits the Notch Transcriptional Activation Complex to Suppress Tumorigenesis**
Luisana Astudillo, Thiago G. Da Silva, Zhiqiang Wang, Xiaoqing Han, Ke Jin, Jeffrey VanWye, Xiaoxia Zhu, Kelly Weaver, Taiji Oashi, Pedro E.M. Lopes, Darren Orton, Leif R. Neitzel, Ethan Lee, Ralf Landgraf, David J. Robbins, Alexander D. MacKerell Jr and Anthony J. Capobianco
Précis: This proof-of-principle study demonstrates that the Notch transcriptional activation complex can be effectively targeted by a small-molecule inhibitor to block aberrant activity and suppress tumor growth, providing a new direction for the development of Notch-based therapeutics.

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TUMOR AND STEM CELL BIOLOGY

3604 MYC-Driven Neuroblastomas Are Addicted to a Telomerase-Independent Function of Dyskerin

Rosemary O'Brien, Sieu L. Tran, Michelle F. Maritz, Bing Liu, Cheng Fei Kong, Stefania Purgato, Chen Yang, Jayne Murray, Amanda J. Russell, Claudia L. Flemming, Georg von Jonquieres, Hilda A. Pickett, Wendy B. London, Michelle Haber, Preethi H. Gunaratne, Murray D. Norris, Giovanni Perini, Jamie I. Fletcher, and Karen L. MacKenzie

Précis: This study suggests an RNA-binding protein called dyskerin may be a point of vulnerability for potential therapeutic exploitation in cancers driven by MYC oncogenes.

3618 Autocrine Secretion of Progastrin Promotes the Survival and Self-Renewal of Colon Cancer Stem-like Cells

Julie Giraud, Laura M. Failla, Jean-Marc Pascussi, Ebba L. Lagerqvist, Jérémy Ollier, Pascal Finetti, François Bertucci, Chu Ya, Imène Gasmî, Jean-François Bourgaux, Michel Prudhomme, Thibault Mazard, Imade Ait-Arsa, Leila Houhou, Daniel Birnbaum, André Pèlerin, Charles Vincent, James G. Ryall, Dominique Joubert, Julie Pannequin, and Frédéric Hollande

Précis: A peptide secreted by colon cancer stem cells appears to function in an autocrine manner to alter metabolism, thereby fueling self-renewal and tumor growth.

3629 Activation of the Lin28/let-7 Axis by Loss of ESE3/EHF Promotes a Tumorigenic and Stem-like Phenotype in Prostate Cancer

Domenico Albino, Gianluca Civenni, Cecilia Dallavalle, Martina Roos, Hartmut Jahns, Laura Curti, Simona Rossi, Sandra Pinton, Gioacchino D'Ambrosio, Fausto Sessa, Jonathan Hall, Carlo V. Catapano, and Giuseppina M. Carbone

Précis: These findings identify a critical barrier to malignant transformation and suggest new strategies to antagonize prostate cancer stem-like cells for therapeutic purposes.

3644 Increased Expression of miR-23a Mediates a Loss of Expression in the RAF Kinase Inhibitor Protein RKIP



Stefan Hatzl, Olivia Geiger, Maja Kim Kuepper, Veronica Caraffini, Till Seime, Tobias Furlan, Erika Nussbaumer, Rotraud Wieser, Martin Pichler, Marcel Scheideler, Katarzyna Nowek, Mojca Jongen-Lavrencic, Franz Quehenberger, Albert Wölfler, Jakob Troppmair, Heinz Sill, and Armin Zebisch

Précis: These findings identify miR-23a as a negative regulator of the metastasis suppressor RKIP in acute myeloid leukemia, with potential therapeutic implications in this and other types of cancer.

CORRECTION

3655 Correction: Mitochondrial Sirtuins in Cancer: Emerging Roles and Therapeutic Potential



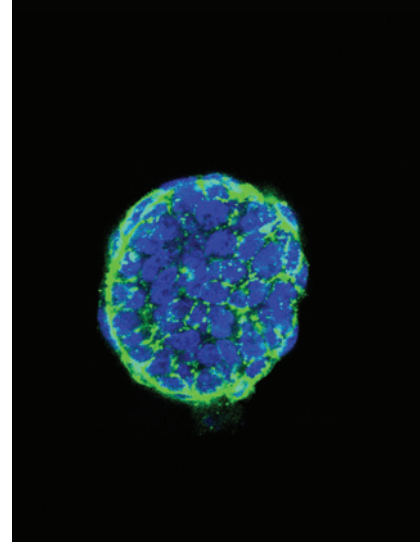
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ABOUT THE COVER

Induced pluripotent stem cells (iPSC) derived from somatic cells of patients hold great promise for autologous cell therapies. Saito and colleagues generated iPSCs from T-cell receptor transgenic T cells, and established a syngeneic preclinical mouse model of evaluating therapeutic efficacy of iPSC-derived T cells. The image depicts immunofluorescence staining of iPSCs for a pluripotency marker, SSEA1 (green), and DAPI (blue). The study found that iPSC-derived T cells exhibit potent antitumor reactivity *in vitro* and *in vivo*. For details, see article by Saito and colleagues on page 3473.



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