

BREAKING ADVANCES

- 3723** Highlights from Recent Cancer Literature

REVIEWS

- 3725** AXL-Driven EMT State as a Targetable Conduit in Cancer
Jane Antony and Ruby Yun-Ju Huang
- 3733** RNA Editing in Pathogenesis of Cancer
Bora E. Baysal, Shraddha Sharma, Seyedhasan Hashemikhabir, and Sarath Chandra Janga

PERSPECTIVE

- 3740** Cancer Cell–Autonomous Parainflammation Mimics Immune Cell Infiltration
Audrey Lasry, Dvir Aran, Atul J. Butte, and Yinon Ben-Neriah

MOLECULAR AND CELLULAR PATHOBIOLOGY

- 3745** Oncogenic RAS Regulates Long Noncoding RNA *Orilnc1* in Human Cancer
Dongmei Zhang, Gao Zhang, Xiaowen Hu, Lawrence Wu, Yi Feng, Sidan He, Youyou Zhang, Zhongyi Hu, Lu Yang, Tian Tian, Weiting Xu, Zhi Wei, Yiling Lu, Keith T. Flaherty, Xiaomin Zhong, Gordon B. Mills, Phyllis A. Gimotty, Xiaowei Xu, Meenhard Herlyn, and Lin Zhang
Précis: RAS-responding effector genes that control cell-cycle transit rely upon coordinate upregulation of a long non-coding RNA, implicating it as a possible therapeutic target in RAS-driven cancers.
- 3758** ETV1-Positive Cells Give Rise to *BRAF*^{V600E}-Mutant Gastrointestinal Stromal Tumors
Leili Ran, Devan Murphy, Jessica Sher, Zhen Cao, Shangqian Wang, Edward Walczak, Youxin Guan, Yuanyuan Xie, Shipra Shukla, Yu Zhan, Cristina R. Antonescu, Yu Chen, and Ping Chi
Précis: This study offers a useful in vivo model of human sporadic forms of *BRAF*-mutant GIST to help unravel its pathogenesis and therapeutic response to novel experimental agents.

TUMOR AND STEM CELL BIOLOGY

- 3766** ATOH1 Promotes Leptomeningeal Dissemination and Metastasis of Sonic Hedgehog Subgroup Medulloblastomas
Katie B. Grausam, Samuel D.R. Dooyema, Laure Bihannic, Hasitha Premathilake, A. Sorana Morrissy, Antoine Forget, Amanda M. Schaefer, Justin H. Gundelach, Slobodan Macura, Diane M. Maher, Xin Wang, Alex H. Heglin, Xijin Ge, Erliang Zeng, Stephanie Puget, Indra Chandrasekar, Kameswaran Surendran, Richard J. Bram, Ulrich Schüller, Michael D. Talyor, Olivier Ayrault, and Haotian Zhao
Précis: These findings illuminate a metastasis pathway in the common pediatric brain tumor medulloblastoma, which offers possible theranostic opportunities.
- 3778** An miRNA Expression Signature for the Human Colonic Stem Cell Niche Distinguishes Malignant from Normal Epithelia
Vignesh Viswanathan, Shirish Damle, Tao Zhang, Lynn Opdenaker, Shirin Modarai, Monica Accerbi, Skye Schmidt, Pamela Green, Deni Galileo, Juan Palazzo, Jeremy Fields, Sepehr Haghghat, Isidore Rigoutsos, Greg Gonye, and Bruce M. Boman
Précis: By defining miRNAs that sustain stem cells in the crypts of normal colon tissue, this study illuminates a pivotal mechanism through which cancer stem-like cells may be created to seed colorectal cancers.
- 3791** Akt Signaling Is Sustained by a CD44 Splice Isoform–Mediated Positive Feedback Loop
Sali Liu and Chonghui Cheng
Précis: This important paper describes the discovery of a positive feedback mechanism that sustains PI3K/Akt signaling in tumor cells that lack PI3K/Akt mutations, illuminating the nearly universal role this pathway has in tumor cell survival.
- 3802** NEMO, a Transcriptional Target of Estrogen and Progesterone, Is Linked to Tumor Suppressor PML in Breast Cancer
Hanan S. Elsarraj, Kelli E. Valdez, Yan Hong, Sandra L. Grimm, Lawrence R. Ricci, Fang Fan, Ossama Tawfik, Lisa May, Therese Cusick, Marc Inciardi, Mark Redick, Jason Gatewood, Onalisa Winblad, Susan Hilsenbeck, Dean P. Edwards, Christy R. Hagan, Andrew K. Godwin, Carol Fabian, and Fariba Behbod
Précis: These findings challenge the notion of the detrimental role of estrogen plus progesterone in breast cancer, revealing a signaling cascade that upregulates the tumor suppressor protein PML in response to both hormones.

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3814 A Systematic Analysis of Oncogenic Gene Fusions in Primary Colon Cancer

Wigard P. Kloosterman,
Robert R.J. Coebergh van den Braak, Mark Pieterse,
Markus J. van Roosmalen, Anieta M. Sieuwerts,
Christina Stangl, Ronne Brunekreef,
Zarina S. Lalmahomed, Salo Ooft, Anne van Galen,
Marcel Smid, Armel Lefebvre, Fried Zwartkruis,
John W.M. Martens, John A. Foekens,
Katharina Biermann, Marco J. Koudijs,
Jan N.M. Ijzermans, and Emile E. Voest

Précis: This deep sequencing study of stage I-III colon cancer specimens identifies novel oncogenic gene fusions in colorectal cancer that may drive malignant progression and offer new targets for personalized therapy.

3823 Mdm2 Is Required for Survival and Growth of p53-Deficient Cancer Cells

Kyle P. Feeley, Clare M. Adams, Ramkrishna Mitra, and Christine M. Eischen

Précis: By refuting the prevailing view that cells lacking Mdm2 can survive if p53 is also absent, this important study provides a therapeutic rationale for targeting Mdm2 to eliminate p53-null lymphomas and sarcomas.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

3834 Therapeutic Rationale to Target Highly Expressed CDK7 Conferring Poor Outcomes in Triple-Negative Breast Cancer

Bo Li, Triona Ni Chonghaile, Yue Fan, Stephen F. Madden, Rut Klinger, Aisling E. O'Connor, Louise Walsh, Gillian O'Hurley, Girish Mallya Udipi, Jesuchristopher Joseph, Finbarr Tarrant, Emer Conroy, Alexander Gaber, Suet-Feung Chin, Helen A. Bardwell, Elena Provenzano, John Crown, Thierry Dubois, Sabine Linn, Karin Jirstrom, Carlos Caldas, Darran P. O'Connor, and William M. Gallagher

Précis: This potentially seminal study offers preclinical proof of concept for combining CDK7 and BCL-2/BCL-XL inhibitors as a mechanism-based therapeutic strategy to improve the management of aggressive triple-negative breast cancers, which still lack effective biomarkers and precision treatment approaches.

3846 Exosome-Derived miR-25-3p and miR-92a-3p Stimulate Liposarcoma Progression

Lucia Casadei, Federica Calore, Chad J. Creighton, Michele Guescini, Kara Batte, O. Hans Iwenofu, Abeba Zewdu, Danielle A. Braggio, Kate Lynn Bill, Paolo Fadda, Francesca Lovat, Gonzalo Lopez, Pierluigi Gasparini, James L. Chen, Raleigh D. Kladney, Gustavo Leone, Dina Lev, Carlo M. Croce, and Raphael E. Pollock

Précis: Two extracellular vesicle-derived microRNAs are found to drive liposarcoma progression by stimulating the secretion of proinflammatory IL6 from tumor-associated macrophages, offering new theranostic opportunities in this cancer setting.

3857 Nicotinic Acid Phosphoribosyltransferase Regulates Cancer Cell Metabolism, Susceptibility to NAMPT Inhibitors, and DNA Repair

Francesco Piacente, Irene Caffa, Silvia Ravera, Giovanna Sociali, Mario Passalacqua, Valerio G. Vellone, Pamela Becherini, Daniele Reverberi, Fiammetta Monacelli, Alberto Ballestrero, Patrizio Odetti, Antonia Cagnetta, Michele Cea, Aimable Nahimana, Michel Duchosal, Santina Bruzzone, and Alessio Nencioni

Précis: Targeting a second enzyme involved in NAD⁺ biosynthesis overcomes the resistance to NAMPT inhibitors observed in clinical trials, offering a path toward new therapies.

3870 CHK1 Inhibition in Small-Cell Lung Cancer Produces Single-Agent Activity in Biomarker-Defined Disease Subsets and Combination Activity with Cisplatin or Olaparib

Triparna Sen, Pan Tong, C. Allison Stewart, Sandra Cristea, Aly Valliani, David S. Shames, Abena B. Redwood, You Hong Fan, Lerong Li, Bonnie S. Glisson, John D. Minna, Julien Sage, Don L. Gibbons, Helen Piwnica-Worms, John V. Heymach, Jing Wang, and Lauren Averett Byers

Précis: These findings demonstrate potent antitumor activity of targeting CHK1 in chemosensitive and chemoresistant models of small cell lung cancer, especially those with MYC amplification or overexpression.

3885 Venetoclax Synergizes with Radiotherapy for Treatment of B-cell Lymphomas

Shyrl O'Steen, Damian J. Green, Ajay K. Gopal, Johnnie J. Orozco, Aimee L. Kenoyer, Yukang Lin, D. Scott Wilbur, Donald K. Hamlin, Darrell R. Fisher, Mark D. Hylarides, Theodore A. Gooley, Amelia Waltman, Brian G. Till, and Oliver W. Press

Précis: Combining the BCL-2 inhibitor venetoclax with radioimmunotherapy yields a synergistic therapeutic response in preclinical models of three lymphoma subtypes, with optimal dosing curing all mice with no detectable toxicity.



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3894 **Oncolytic Adenovirus and Tumor-Targeting Immune Modulatory Therapy Improve Autologous Cancer Vaccination**



Hong Jiang, Yisel Rivera-Molina, Candelaria Gomez-Manzano, Karen Clise-Dwyer, Laura Bover, Luis M. Vence, Ying Yuan, Frederick F. Lang, Carlo Toniatti, Mohammad B. Hossain, and Juan Fueyo

Précis: Combining an oncolytic virus with an immune checkpoint drug creates an in situ autologous vaccine effect, establishing a tumor-specific treatment that is both efficacious and durable.

3942 **Highly Accurate Detection of Cancer *In Situ* with Intraoperative, Label-Free, Multimodal Optical Spectroscopy**

Michael Jermyn, Jeanne Mercier, Kelly Aubertin, Joannie Desroches, Kirk Urme, Jason Karamchandiani, Eric Marple, Marie-Christine Guiot, Frederic Leblond, and Kevin Petrecca

Précis: These findings present the design, development, and clinical testing of a cancer detection system of nearly perfect accuracy that can improve surgical resections while in the operating room.

INTEGRATED SYSTEMS AND TECHNOLOGIES

3908 **Pharmacokinetics and Drug Interactions Determine Optimum Combination Strategies in Computational Models of Cancer Evolution**



Shaon Chakrabarti and Franziska Michor

Précis: In seeking to improve responses to combination therapy, a model that incorporates parameters for cancer evolution suggests variations in dosing regimens that can safely increase therapeutic efficacy, with immediate clinical implications.

3922 **Somatic Mutations Drive Distinct Imaging Phenotypes in Lung Cancer**



Emmanuel Rios Velazquez, Chintan Parmar, Ying Liu, Thibaud P. Coroller, Gisele Cruz, Olya Stringfield, Zhaoxiang Ye, Mike Makrigiorgos, Fiona Fennessy, Raymond H. Mak, Robert Gillies, John Quackenbush, and Hugo J.W.L. Aerts

Précis: The findings of this important study add to the understanding of the biological basis for tumor phenotypes, which can be quantified by medical imaging.

3931 **Noninvasive Interrogation of DLL3 Expression in Metastatic Small Cell Lung Cancer**

Sai Kiran Sharma, Jacob Pourat, Dalya Abdel-Atti, Sean D. Carlin, Alessandra Piersigilli, Alexander J. Bankovich, Eric E. Gardner, Omar Hamdy, Kumiko Isse, Sheila Bheddah, Joseph Sandoval, Kristen M. Cunanan, Eric B. Johansen, Viola Allaj, Vikram Sisodiya, David Liu, Brian M. Zeglis, Charles M. Rudin, Scott J. Dylla, John T. Poirier, and Jason S. Lewis

Précis: A companion diagnostic PET imaging agent can enable clinicians to rapidly identify small cell lung cancer patients most likely to benefit from treatment with a Notch ligand-targeting therapy, despite low levels of ligand expression on the surface of the cancer cells.

PREVENTION AND EPIDEMIOLOGY

3951 **Androgens Are Differentially Associated with Ovarian Cancer Subtypes in the Ovarian Cancer Cohort Consortium**

Jennifer Ose, Elizabeth M. Poole, Helena Schock, Matti Lehtinen, Alan A. Arslan, Anne Zeleniuch-Jacquotte, Kala Visvanathan, Kathy Helzlsouer, Julie E. Buring, I-Min Lee, Anne Tjønneland, Laure Dossus, Antonia Trichopoulou, Giovanna Masala, N. Charlotte Onland-Moret, Elisabete Weiderpass, Eric J. Duell, Annika Idahl, Ruth C. Travis, Sabina Rinaldi, Melissa A. Merritt, Britton Trabert, Nicolas Wentzensen, Shelley S. Tworoger, Rudolf Kaaks, and Renée T. Fortner

Précis: These findings show significant differences in the associations between circulating androgen concentrations and invasive ovarian cancer risk by subtype, underscoring the importance of examining etiologic differences by subtype.

CORRECTIONS

3961 **Correction: MYC Mediates Large Oncosome-Induced Fibroblast Reprogramming in Prostate Cancer**

3962 **Correction: Wnt5a Drives an Invasive Phenotype in Human Glioblastoma Stem-like Cells**



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ABOUT THE COVER

The image shows a single breast tumor tissue core derived from a tissue microarray of patients with triple-negative breast cancer that was immunohistochemically stained with an anti-CDK7 antibody. Brown staining in cell nuclei represents positive expression of CDK7 protein, allowing for further analysis of CDK7 positivity using a nuclear algorithm. The stained tumor tissue was recorded using a digital slide scanning device. For details, see article by Li and colleagues on page 3834.



Cancer Research

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

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