

BREAKING ADVANCES

- 1507** Highlights from Recent Cancer Literature

PERSPECTIVE

- 1510** Precancer Atlas to Drive Precision Prevention Trials
Avrum Spira, Matthew B. Yurgelun, Ludmil Alexandrov, Anjana Rao, Rafael Bejar, Kornelia Polyak, Marios Giannakis, Ali Shilatifard, Olivera J. Finn, Madhav Dhodapkar, Neil E. Kay, Esteban Braggio, Eduardo Vilar, Sarah A. Mazzilli, Timothy R. Rebbeck, Judy E. Garber, Victor E. Velculescu, Mary L. Disis, Douglas C. Wallace, and Scott M. Lippman

REVIEWS

- 1542** The Role of PIAS SUMO E3-Ligases in Cancer
Andrea Rabellino, Cristina Andreani, and Pier Paolo Scaglioni
- 1548** Surgery for Cancer: A Trigger for Metastases
Samer Tohme, Richard L. Simmons, and Allan Tsung

INTEGRATED SYSTEMS AND TECHNOLOGIES

- 1553** Therapeutic Potential of Bacteria against Solid Tumors
Haralampos Hatzikirou, Juan Carlos López Alfonso, Sara Leschner, Siegfried Weiss, and Michael Meyer-Hermann
Précis: Combined in vivo murine experiments and mathematical modeling provide a mechanistic understanding of the therapeutic potential of bacterial infections against solid tumors.
- 1564** Modeling the Genetic Regulation of Cancer Metabolism: Interplay between Glycolysis and Oxidative Phosphorylation
 Linglin Yu, Mingyang Lu, Dongya Jia, Jianpeng Ma, Eshel Ben-Jacob, Herbert Levine, Benny Abraham Kaiparettu, and José N. Onuchic
Précis: A systems approach illuminates the enhanced metabolic plasticity of cancer cells, providing a platform for designing combination cancer therapies to effectively and selectively target cancer cell metabolism.

- 1575** Bayesian Network Inference Modeling Identifies TRIB1 as a Novel Regulator of Cell-Cycle Progression and Survival in Cancer Cells


Rina Gendelman, Heming Xing, Olga K. Mirzoeva, Preeti Sarde, Christina Curtis, Heidi S. Feiler, Paul McDonagh, Joe W. Gray, Iya Khalil, and W. Michael Korn

Précis: Unbiased interrogation of complex cellular signal transduction circuits in response to MEK inhibition identifies novel factors that represent potential novel therapeutic targets.

MICROENVIRONMENT AND IMMUNOLOGY

- 1586** Scavenger Receptor A1 Prevents Metastasis of Non–Small Cell Lung Cancer via Suppression of Macrophage Serum Amyloid A1
Yan Zhang, Yongyue Wei, Bin Jiang, Lili Chen, Hui Bai, Xudong Zhu, Xiaoyu Li, Hanwen Zhang, Qing Yang, Junqing Ma, Yong Xu, Jingjing Ben, David C. Christiani, and Qi Chen
Précis: These findings define a prognostic biomarker in lung adenocarcinoma and establish a functional rationale for its future assessment as a therapeutic target.
- 1599** Myeloid Cells That Impair Immunotherapy Are Restored in Melanomas with Acquired Resistance to BRAF Inhibitors
Shannon M. Steinberg, Tamer B. Shabaneh, Peisheng Zhang, Viktor Martyanov, Zhenghui Li, Brian T. Malik, Tamara A. Wood, Andrea Boni, Aleksey Molodtsov, Christina V. Angeles, Tyler J. Curiel, Michael L. Whitfield, and Mary Jo Turk
Précis: These results illustrate how extrinsic pathways of immunosuppression governed by melanoma cells dominate the tumor microenvironment, highlighting the need to target extrinsic as well as intrinsic mechanisms of drug resistance.
- 1611** Enriching the Housing Environment for Mice Enhances Their NK Cell Antitumor Immunity via Sympathetic Nerve–Dependent Regulation of NKG2D and CCR5
Yanfang Song, Yu Gan, Qing Wang, Zihong Meng, Guohua Li, Yuling Shen, Yufeng Wu, Peiying Li, Ming Yao, Jianren Gu, and Hong Tu
Précis: These findings provide mechanistic insight into how positive stress (termed eustress) restrains malignant development and progression, opening up new perspectives on cancer prevention and treatment.

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- 1623** Broad and Conserved Immune Regulation by Genetically Heterogeneous Melanoma Cells
Natalie J. Neubert, Laure Tillé, David Barras, Charlotte Soneson, Petra Baumgaertner, Donata Rimoldi, David Gfeller, Mauro Delorenzi, Silvia A. Fuertes Marraco, and Daniel E. Speiser

Précis: Despite their high genetic heterogeneity, human melanoma cells show conserved and predominantly homogenous immune gene regulation in response to CTL-based immunotherapy.

MOLECULAR AND CELLULAR PATHOBIOLOGY

- 1637** YAP/TAZ-Mediated Upregulation of GAB2 Leads to Increased Sensitivity to Growth Factor–Induced Activation of the PI3K Pathway
Chao Wang, Chao Gu, Kang Jin Jeong, Dong Zhang, Wei Guo, Yiling Lu, Zhenlin Ju, Nattapon Panupinthu, Ji Yeon Yang, Mihai (Mike) Gagea, Patrick Kwok Shing Ng, Fan Zhang, and Gordon B. Mills

Précis: Interactions between HIPPO, YAP/TAZ, and the PI3K/AKT pathway may be therapeutically targetable, providing new approaches to treating endometrial cancers and other cancers where the HIPPO pathway is a core oncogenic driver.

- 1649** SDHD Promoter Mutations Ablate GABP Transcription Factor Binding in Melanoma
Tongwu Zhang, Mai Xu, Matthew M. Makowski, Christine Lee, Michael Kovacs, Jun Fang, Esther Willems, Jeffrey M. Trent, Nicholas K. Hayward, Michiel Vermeulen, and Kevin M. Brown

Précis: These findings define the effects of mutations in a succinate dehydrogenase complex component implicated in the pathogenesis of ~5% of metastatic melanomas.

- 1662** CYP27A1 Loss Dysregulates Cholesterol Homeostasis in Prostate Cancer
Mahmoud A. Alfaqih, Erik R. Nelson, Wen Liu, Rachid Safi, Jeffery S. Jasper, Everardo Macias, Joseph Geradts, J. Will Thompson, Laura G. Dubois, Michael R. Freeman, Ching-yi Chang, Jen-Tsan Chi, Donald P. McDonnell, and Stephen J. Freedland

Précis: Bioinformatics identify CYP27A1, a key cellular cholesterol sensor, as a critical downregulated gene in prostate cells, contributing to their pathogenesis.

PREVENTION AND EPIDEMIOLOGY

- 1674** Correlates of Prenatal and Early-Life Tobacco Smoke Exposure and Frequency of Common Gene Deletions in Childhood Acute Lymphoblastic Leukemia
Adam J. de Smith, Maneet Kaur, Semira Gonseth, Alyson Endicott, Steve Selvin, Luoping Zhang, Ritu Roy, Xiaorong Shao, Helen M. Hansen, Alice Y. Kang, Kyle M. Walsh, Gary V. Dahl, Roberta McKean-Cowdin, Catherine Metayer, and Joseph L. Wiemels

Précis: This epidemiological study finds that tobacco smoke exposure is associated with increased frequency of somatic gene deletions in childhood ALL, linking parental smoking with the most common type of childhood cancer.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

- 1684** Prolactin Receptor–Mediated Internalization of Imaging Agents Detects Epithelial Ovarian Cancer with Enhanced Sensitivity and Specificity
Karthik M. Sundaram, Yilin Zhang, Anirban K. Mitra, Jean-Louis K. Kouadio, Katja Gwin, Anthony A. Kossiakoff, Brian B. Roman, Ernst Lengyel, and Joseph A. Piccirilli

Précis: This study establishes a targeted, noninvasive imaging approach for the detection of ovarian cancer tumors with high sensitivity and specificity by exploiting the ability of the prolactin receptor to endocytose specific imaging conjugates.

- 1697** FLT3 and JAK2 Mutations in Acute Myeloid Leukemia Promote Interchromosomal Homologous Recombination and the Potential for Copy Neutral Loss of Heterozygosity
 Terry J. Gaymes, Azim Mohamedali, Anthony L. Eiliazadeh, David Darling, and Ghulam J. Mufti

Précis: These findings suggest that antioxidant treatment of FLT3-mutant acute myeloid leukemias can hinder the acquisition of genomic instability and thereby slow leukemic progression.

- 1709** Chemosensitivity of IDH1-Mutated Gliomas Due to an Impairment in PARP1-Mediated DNA Repair
Yanxin Lu, Jakub Kwintkiewicz, Yang Liu, Katherine Tech, Lauren N. Frady, Yu-Ting Su, Wendy Bautista, Seog In Moon, Jeffrey MacDonald, Matthew G. Ewend, Mark R. Gilbert, Chunzhang Yang, and Jing Wu

Précis: Low-grade gliomas harbor a targetable metabolic deficiency that compromises a critical mechanism of DNA repair, with implications for therapeutic management of these tumors.

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TUMOR AND STEM CELL BIOLOGY

1719 Systematic *In Vivo* Inactivation of Chromatin-Regulating Enzymes Identifies Setd2 as a Potent Tumor Suppressor in Lung Adenocarcinoma

David M. Walter, Olivia S. Venancio, Elizabeth L. Buza, John W. Tobias, Charuhas Deshpande, A. Andrea Gudiel, Caroline Kim-Kiselak, Michelle Cicchini, Travis J. Yates, and David M. Feldser

Précis: These findings establish a novel potent tumor suppressor in lung adenocarcinoma, shedding light on how chromatin dysregulation promotes lung cancer progression.

1730 Somatic Ephrin Receptor Mutations Are Associated with Metastasis in Primary Colorectal Cancer



Lucy Mathot, Snehangshu Kundu, Viktor Ljungström, Jessica Svedlund, Lotte Moens, Tom Adlerteg, Elin Falk-Sörqvist, Verónica Rendo, Claudia Bellomo, Markus Mayrhofer, Carme Cortina, Magnus Sundström, Patrick Micke, Johan Botling, Anders Isaksson, Aristidis Moustakas, Eduard Batlle, Helgi Birgisson, Bengt Glimelius, Mats Nilsson, and Tobias Sjöblom

Précis: Colorectal cancer metastasis is linked to somatic mutations in Eph receptor tyrosine kinases, with implications to improve patient stratification and choice of therapy in primary colon cancer cases.

1741 Membrane-Depolarizing Channel Blockers Induce Selective Glioma Cell Death by Impairing Nutrient Transport and Unfolded Protein/Amino Acid Responses

Mia Niklasson, Gianluca Maddalo, Zuzana Sramkova, Ercan Mutlu, Shimei Wee, Petra Sekyrova, Linnéa Schmidt, Nicolas Fritz, Ivar Dehnisch, Gregorios Kyriatzis, Michaela Krafcikova, Brittany B. Carson, Jennifer M. Feenstra, Voichita D. Marinescu, Anna Segerman, Martin Haraldsson, Anna-Lena Gustavsson, Lars G.J. Hammarström, Annika Jenmalm Jensen, Lene Uhrbom, A.F. Maarten Altelaar, Sten Linnarsson, Per Uhlén, Lukas Trantirek, C. Theresa Vincent, Sven Nelander, Per Øyvind Enger, and Michael Andäng

Précis: Use of an integrated approach to study weaknesses in glioma-initiating cells identifies bioelectric function as a possible Achilles' heel in glioblastoma, with implications for improving its therapeutic management.

1753 Histone Acetyltransferase Activity of MOF Is Required for *MLL-AF9* Leukemogenesis

Daria G. Valerio, Haiming Xu, Chun-Wei Chen, Takayuki Hoshii, Meghan E. Eisold, Christopher Delaney, Monica Cusan, Aniruddha J. Deshpande, Chun-Hao Huang, Amaia Lujambio, Yujun George Zheng, Johannes Zuber, Tej K. Pandita, Scott W. Lowe, and Scott A. Armstrong

Précis: These findings offer a mechanistic rationale to inhibit MOF acetyltransferase activity as a therapeutic strategy to treat aggressive *MLL*-rearranged leukemias.

1763 Oncogenic Effects of High MAPK Activity in Colorectal Cancer Mark Progenitor Cells and Persist Irrespective of RAS Mutations

Cristina Blaj, Eva Marina Schmidt, Sebastian Lamprecht, Heiko Hermeking, Andreas Jung, Thomas Kirchner, and David Horst

Précis: Cancer stem-like cells in heterogeneous colon tumors can maintain their regulation of MAPK signaling pathways whether or not *KRAS* mutations are present.

LETTERS TO THE EDITOR

1775 EGFR-Dependent Regulated Intramembrane Proteolysis of EpCAM—Letter

Olivier Gires

1777 EGFR-Dependent Regulated Intramembrane Proteolysis of EpCAM—Response

Ya-Ting Hsu, Pawel Osmulski, Yao Wang, Yi-Wen Huang, Lu Liu, Jianhua Ruan, Victor X. Jin, Nameer B. Kirma, Maria E. Gaczynska, and Tim Hui-Ming Huang

CORRECTIONS

1778 Correction: EpCAM-Regulated Transcription Exerts Influences on Nanomechanical Properties of Endometrial Cancer Cells That Promote Epithelial-to-Mesenchymal Transition

1779 Correction: Efficacy of Cotargeting Angiopoietin-2 and the VEGF Pathway in the Adjuvant Postsurgical Setting for Early Breast, Colorectal, and Renal Cancers

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ABOUT THE COVER

Mice housed in an enriched environment display a remarkable antitumor phenotype. Enriching the housing conditions for mice enhances the tumor infiltration and the cytotoxicity ability of natural killer (NK) cells via sympathetic nerve-dependent regulation of NKG2D and CCR5 expressions on NK cells. The immunohistochemical staining for NK1.1 shows an increased number of infiltrating NK cells in transplanted tumors from enriched environment-housed mice. For details, see article by Song and colleagues on page 1611.

