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Anna Juncker-Jensen, Elena I. Deryugina, Ivo Rimann, Ewa Zajac, Tatjana A. Kupriyanova, Lars H. Engellholm, and James P. Quigley

Précis: Therapeutic targeting of a newly unraveled tumor pathway with connections to a thrombin receptor on endothelial cells is effective in preventing carcinoma cell intravasation, the earliest step of tumor metastasis.

4196 VEGF-C and VEGF-D Blockade Inhibits Inflammatory Skin Carcinogenesis
Annamari K. Alitalo, Steven T. Proulx, Sinem Karaman, David Abercusher, Stefania Martino, Manuela Jost, Nicole Schneider, Maija Bry, and Michael Detmar

Précis: These findings show that less-studied isoforms of VEGF shape the inflammatory tumor microenvironment and support the use of VEGF-C/D antagonists to inhibit both early and late stages of tumor growth.

4196 Intestinal Bacteria Modify Lymphoma Incidence and Latency by Affecting Systemic Inflammatory State, Oxidative Stress, and Leukocyte Genotoxicity
Mitsuko L. Yamamoto, Irene Maier, Angeline Tilly Dang, David Berry, Jared Liu, Paul M. Ruegger, Jue-in Yang, Philip A. Soto, Laura L. Presley, Ramune Reliene, Aya M. Westbrook, Bo Wei, Alexander Loy, Christopher Chang, Jonathan Braun, James Borneman, and Robert H. Schiestl

Précis: This potentially seminal study reveals the powerful effects that intestinal microbiota can exert on lymphoma penetrance in genetically susceptible mice, with possible implications for preventing this cancer in individuals who are at risk of disease.

4196 Bone Marrow–Derived CD11b–Jagged2⁺ Cells Promote Epithelial-to-Mesenchymal Transition and Metastasization in Colorectal Cancer
Francisco Caiado, Tânia Carvalho, Isadora Rosa, Leonor Remédio, Ana Costa, João Matos, Beate Heissig, Hideo Yagita, Koichi Hattori, João Pereira da Silva, Paulo Fidalgo, António Dias Pereira, and Sérgio Dias

Précis: These findings suggest that quantifying the number of circulating bone marrow cells expressing JAG2 might define metastatic development in colorectal cancer patients.
Rb1 Haploinsufficiency Promotes Telomere Attrition and Radiation-Induced Genomic Instability
Iria Gonzalez-Vasconcellos, Natasa Anastasov, Bahar Sanli-Bonazzi, Olena Klymenko, Michael J. Atkinson, and Michael Rosemann

Précis: These findings suggest that telomere maintenance is a noncanonical caretaker function of the retinoblastoma protein, such that its deficiency in cancer may act beyond simply deregulating cell-cycle control.

4256
Extracellular DNA in Pancreatic Cancer Promotes Cell Invasion and Metastasis
Fushi Wen, Alex Shen, Andrew Choi, Eugene W. Gerner, and Jiaqi Shi

Précis: This study offers a provocative set of observations, suggesting that the accumulation of extracellular DNA in the microenvironment of pancreatic tumors triggers a feed-forward inflammatory signal that strongly promotes invasive and metastatic behavior.

4267
Radioresistant Cancer Cells Can Be Conditioned to Enter Senescence by mTOR Inhibition
Hae Yun Nam, Myung Woal Han, Hyo Won Chang, Yoon Sun Lee, Myungjin Lee, Hyung Ju Lee, Young Wook Lee, Hee Jin Lee, Kyung Eun Lee, Min Kyo Jung, Hyesung Jeon, Seung-Ho Choi, Neung Hwa Park, Sang Yoon Kim, and Seong Who Kim

Précis: By revealing that mTOR inhibition can promote cellular senescence in radio-resistant cancer cells through activation of the RB pathway, this study provides a novel mechanistic perspective on how mTOR inhibitors can be used combinatorially to improve cancer therapy.

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PML-RARα and Its Phosphorylation Regulate PML Oligomerization and HIPK2 Stability
Yutaka Shima, Yuki Honma, and Issay Kitabayashi

Précis: These findings offer mechanistic insights into the basis for the most common prodifferentiation therapies used to treat acute promyelocytic leukemia in the clinic.

4289
HMGA2 Is a Driver of Tumor Metastasis
Asahiro Morishita, M. Raza Zaidi, Akira Mitoro, Devipriya Sankarasharma, Matthias Szabolcs, Yasunori Okada, Jeanine D'Armiento, and Kiran Chada

Précis: These results define a key function in cancer invasion and metastasis for a nonhistone chromatin-binding protein that activates EMT by upregulating the TGFβ signaling pathway.
4349  PPARγ Induces Estrogen Receptor-Positive Mammary Neoplasia through an Inflammatory and Metabolic Phenotype Linked to mTOR Activation
Hongyan Yuan, Jin Lu, Junfeng Xiao, Geeta Upadhay, Rachel Umans, Bhaskar Kallakury, Yuuki Yin, Michael E. Fant, Levie Kopelowich, and Robert L. Glazer

4383  Therapeutic Destruction of Insulin Receptor Substrates for Cancer Treatment
Hadass Reuveni, Efrat Flashner-Abramson, Lilach Steiner, Kirill Makedonski, Renduo Song, Alexei Shir, Meenhard Herlyn, Menashe Bar-Eli, and Alexander Levitzki

4395  4-Hydroxytamoxifen Induces Autophagic Death through K-Ras Degradation
Latika Kohli, Niroop Kaza, Tatjana Coric, Stephanie J. Byer, Nicole M. Brossier, Barbara J. Klocke, Mary-Ann Bjornsti, Steven L. Carroll, and Kevin A. Roth

4406  KEAP1 Is a Redox Sensitive Target That Arbitrates the Opposing Radiosensitive Effects of Parthenolide in Normal and Cancer Cells
Yong Xu, Fang Fang, Sumitra Miriyala, Peter A. Crooks, Terry D. Oberley, Lukasana Chaiswing, Teresa Noel, Aaron K. Holley, Yanning Zhao, Kelley K. Kinningham, Daret K. St. Clair, and William H. St. Clair

4418  Very low-dose radiation used increasingly in imaging tumors subjected to irradiation is reported in this study to trigger adaptive responses that could adversely affect treatment outcomes, a possibility requiring attention by radiation oncologists.

4429  Metformin Decreases Glucose Oxidation and Increases the Dependency of Prostate Cancer Cells on Reductive Glutamine Metabolism
Sarah-Maria Fendt, Eric L. Bell, Mark A. Keibler, Gregory J. Wirth, Brian Fiske, Jared R. Mayers, Matthias Schwab, Gary Bellinger, Alfredo Csibi, Akash Patnaik, Marie Jose Blouin, Lewis C. Cantley, Harold G. Sutton, Jian Jian Li, Gayle E. Woloschak, and Ralph R. Weichselbaum

4460  A novel mechanism of autophagic death triggered by tamoxifen in tumor cells may make this common breast cancer drug more broadly useful in cancer therapy.
### Antitumor Activity of a Humanized, Bivalent Immunotoxin Targeting Fn14-Positive Solid Tumors

Hong Zhou, Walter N. Hittelman, Hideo Yagita, Lawrence H. Cheung, Stuart S. Martin, Jeffrey A. Winkles, and Michael G. Rosenblum

**Précis:** These findings offer a preclinical proof of concept for the use of an immune targeting principle that may be both highly specific to cancer and broadly applicable to many different disease types.

### Visualizing Inhibition of Nucleosome Mobility and Transcription by Cisplatin–DNA Interstrand Crosslinks in Live Mammalian Cells

Guangyu Zhu, Lina Song, and Stephen J. Lippard

**Précis:** A minor DNA adduct formed by cisplatin may confer the most significant effects of this drug on tumor cells, as revealed by this study of nucleosome structure and DNA transcription in live cells.

### CX3CL1 Promotes Breast Cancer via Transactivation of the EGF Pathway

Mannel Tardáguila, Emilia Mira, Miguel A. Garcia-Cabezas, Anna M. Feijoo, Miguel Quintela-Fandino, Íñigo Azcuita, Sergio A. Lira, and Santos Mañes

**Précis:** A chemokine that is induced by IL-1, a central proinflammatory cytokine in the tumor microenvironment, promotes HER2+ breast cancers by supporting expression of the EGF receptor.

### β-Catenin Signaling Is a Critical Event in ErbB2-Mediated Mammary Tumor Progression

Babette Schade, Robert Lesurf, Virginie Sanguin-Gendreau, Tung Bui, Geneviève Deblois, Sandra A. O'Toole, Ewan K.A. Millar, Sara J. Zardawi, Elena Lopez-Knowles, Robert L. Sutherland, Vincent Giguère, Michael Kahn, Michael Hallett, and William J. Muller

**Précis:** A mouse model that faithfully recapitulates many genetic features of the basal subset of ErbB2-positive breast cancers identifies the Wnt pathway as an essential driver and candidate therapeutic target for this aggressive disease.

### EYA1 Phosphatase Function Is Essential to Drive Breast Cancer Cell Proliferation through Cyclin D1

Kongming Wu, Zhaoming Li, Shaoxin Cai, Lifeng Tian, Ke Chen, Jing Wang, Junbo Hu, Ye Sun, Xue Li, Adam Ertel, and Richard G. Pestell

**Précis:** The homolog of a fruitfly regulator of retinal development that is overexpressed in the luminal B subtype of breast cancers appears to be an essential pathogenic driver in this setting, with implications in other cancers where this regulator is also overexpressed.

### Microtubule-Associated Histone Deacetylase 6 Supports the Calcium Store Sensor STIM1 in Mediating Malignant Cell Behaviors


**Précis:** Targeting calcium-based cellular physiology offers an appealing general strategy to disrupt cancer cell function, if a disease-specific approach can be identified.

### EYA1 Phosphatase Function Is Essential to Drive Breast Cancer Cell Proliferation through Cyclin D1

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**Précis:** The homolog of a fruitfly regulator of retinal development that is overexpressed in the luminal B subtype of breast cancers appears to be an essential pathogenic driver in this setting, with implications in other cancers where this regulator is also overexpressed.

### c-Src Modulates Estrogen-Induced Stress and Apoptosis in Estrogen-Deprived Breast Cancer Cells

Ping Fan, Obi L. Griffith, Fadeke A. Agboke, Pavana Anur, Xiaojun Zou, Russell E. McDaniel, Karen Creswell, Sung Hoon Kim, John A. Katzenellenbogen, Joe W. Gray, and V. Craig Jordan

**Précis:** In revealing a role for c-Src tyrosine kinase in estrogen-induced apoptosis, this study offers a mechanistic rationale for a new approach in the treatment of endocrine-resistant breast cancer.

### The ShcA PTB Domain Functions as a Biological Sensor of Phosphotyrosine Signaling during Breast Cancer Progression

Byuhjin Ahn, Valerie Sabourin, Jacqueline R. Ha, Sean Cory, Gordana Maric, Young Kyuen Im, W. Rod Hardy, Hong Zhao, Morag Park, Michael Hallett, Peter M. Siegel, Tony Pawson, and Josie Ursini-Siegel

**Précis:** In the receptor tyrosine kinase adapter protein Shc, the phosphotyrosine-binding PTB domain rather than the SH2 domain appears to be the critical intersection for transmitting effector signals that control breast cancer development.
ETS Transcription Factor ESE1/ELF3 Orchestrates a Positive Feedback Loop That Constitutively Activates NF-κB and Drives Prostate Cancer Progression
Nicole Longoni, Manuela Sarti, Domenico Albino, Gianluca Civenni, Anastasia Malek, Erica Ortelii, Sandra Pinton, Maurizia Mello-Grand, Paola Ostano, Gisacchino D'Ambrosio, Fausto Sessa, Ramon Garcia-Escudero, George N. Thalmann, Giovanna Chiorino, Carlo V. Catapano, and Giuseppina M. Carbone

Précis: In extending the importance of ETS transcription functions in prostate cancer, this study defines an important new mechanism connecting inflammatory signaling, NF-κB activation, and prostate cancer progression.

Vitronectin–αvβ3 Integrin Engagement Directs Hypoxia-Resistant mTOR Activity and Sustained Protein Synthesis Linked to Invasion by Breast Cancer Cells
Carolina Pola, Silvia C. Formenti, and Robert J. Schneider

Précis: These findings suggest a mechanistic rationale to target a nodal driver of breast cancer invasion to bone, in a hypoxic tissue microenvironment where this common but little-understood step in progression occurs.

Gankyrin Activates IL-8 to Promote Hepatic Metastasis of Colorectal Cancer
Zhaofang Bai, Yanhong Tai, Weihua Li, Cheng Zhen, Weiting Gu, Zhao Jian, Qianyi Wang, Jieru E. Lin, Qing Zhao, Weili Gong, Bing Liang, Chenguang Wang, and Tao Zhou

Précis: This potentially seminal study suggests readily tractable targets to prevent or treat hepatic metastasis of colorectal cancer, the chief form of the advanced state in this disease.

Chromatin Regulator PRC2 Is a Key Regulator of Epigenetic Plasticity in Glioblastoma
Atsushi Natsume, Motokazu Ito, Keisuke Katsushima, Fumiharu Ohka, Akira Hatanaka, Keiko Shinjo, Shinya Sato, Satoru Takahashi, Yuta Ishikawa, Ichiro Takeuchi, Hiroki Shimogawa, Motonari Uesugi, Hideyuki Okano, Seung U. Kim, Toshihiko Wakabayashi, Jean-Pierre J. Issa, Yoshitaka Sekido, and Yutaka Kondo

Précis: A modifier complex that controls tumor cell plasticity may provide a target to restrict the functional heterogeneity in tumors, a core challenge to all cancer cell-centric drugs, given the huge reservoir of resistance mechanisms that such heterogeneity confers.

LETTERS TO THE EDITOR

Tumor Growth Control with IDO-Silencing Salmonella—Letter
Robert M. Hoffman

Tumor Growth Control with IDO-Silencing Salmonella—Reply
Edwin R. Manuel, Bruce R. Blazar, and Don J. Diamond

CORRECTION

Correction: Critical Role for the Receptor Tyrosine Kinase EPHB4 in Esophageal Cancers
ABOUT THE COVER

β-catenin is a multifunctional protein that plays a vital structural role in cadherin-based cell adhesion and is an important transcriptional activator of canonical Wnt-mediated gene expression. Dysregulation or mutational activation of the β-catenin signaling is a critical event in the development of human cancer, including breast cancer. Immunofluorescence staining was used to visualize localization of β-catenin and activated β-catenin in human ERBB2-overexpressing ER-negative breast cancer cells (HCC202). The presence of nuclear-activated β-catenin in these breast cancer cells was correlated with a decrease in cell proliferation upon inhibition of β-catenin signaling. For details, see article by Schade and colleagues on page 4474.

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