

BREAKING ADVANCES

- 6539 | **Highlights from Recent Cancer Literature**

REVIEWS

- 6541 | **Targeting microRNAs in Pancreatic Cancer: Microplayers in the Big Game**
Sheema Khan, Ansarullah, Deepak Kumar, Meena Jaggi, and Subhash C. Chauhan
- 6548 | **Cancerous Inhibitor of Protein Phosphatase 2A, an Emerging Human Oncoprotein and a Potential Cancer Therapy Target**
Anchit Khanna, John E. Pimanda, and Jukka Westermarck
- 6554 | **miRNA Dysregulation in Breast Cancer**
Laoighse Mulrane, Sharon F. McGee, William M. Gallagher, and Darran P. O'Connor

INTEGRATED SYSTEMS AND TECHNOLOGIES

- 6563 | **A DNA Methylation Prognostic Signature of Glioblastoma: Identification of NPTX2-PTEN-NF- κ B Nexus**
Sudhanshu Shukla, Irene Rosita Pia Patric, Sivaarumugam Thinagararjan, Sujaya Srinivasan, Baisakhi Mondal, Alangar S. Hegde, Bangalore A. Chandramouli, Vani Santosh, Arimappamagan Arivazhagan, and Kumaravel Somasundaram
- Précis:* This study of global DNA methylation in the most deadly form of brain cancer reveals a simple prognostic marker, with potential implications for treatment.

MICROENVIRONMENT AND IMMUNOLOGY

- 6574 | **Parathyroid Hormone-Related Protein Drives a CD11b⁺Gr1⁺ Cell-Mediated Positive Feedback Loop to Support Prostate Cancer Growth**
Serk In Park, Changki Lee, W. David Sadler, Amy J. Koh, Jacqueline Jones, Jung Won Seo, Fabiana N. Soki, Sun Wook Cho, Stephanie D. Daignault, and Laurie K. McCauley
- Précis:* A cancer cell-secreted bone regulatory factor promoting hypercalcemia has a pivotal role in recruiting a class of immune-suppressor cells that drive tumor angiogenesis and progression.

- 6584 | **Soluble Carcinoembryonic Antigen Activates Endothelial Cells and Tumor Angiogenesis**



Kira H. Bramswig, Marina Poettler, Matthias Unseld, Friedrich Wrba, Pavel Uhrin, Wolfgang Zimmermann, Christoph C. Zielinski, and Gerald W. Prager

Précis: These findings define a functional role in tumor angiogenesis for a serum biomarker used widely in the oncology clinic to monitor the growth of many cancers.

- 6597 | **Adjuvants That Improve the Ratio of Antigen-Specific Effector to Regulatory T Cells Enhance Tumor Immunity**

Rachel Perret, Sophie R. Sierro, Natalia K. Botelho, Stéphanie Cognac, Alena Donda, and Pedro Romero

Précis: These findings may improve the design of effective cancer vaccines by advancing understanding of the interactions of different vaccine components and immune cell types.

- 6609 | **Enhancement of Antitumor Immunity in Lung Cancer by Targeting Myeloid-Derived Suppressor Cell Pathways**



Anandi Sawant, Cara C. Schafer, Tong Huan Jin, Jaroslaw Zmijewski, Hubert M. Tse, Justin Roth, Zhihuan Sun, Gene P. Siegal, Victor J. Thannickal, Stefan C. Grant, Selvarangan Ponnazhagan, and Jessy S. Deshane

Précis: This study identifies a novel therapeutic strategy to overcome tumoral immunosuppression in lung cancer, opening new routes to trigger regression and prevent relapses in this disease.

MOLECULAR AND CELLULAR PATHOBIOLOGY

- 6621 | **Genetic and Pharmacologic Inhibition of mTORC1 Promotes EMT by a TGF- β -Independent Mechanism**

Ivan Mikaelian, Mouhannad Malek, Rudy Gadet, Jean Viallet, Amandine Garcia, Anaïs Girard-Gagnepain, Cédric Hesling, Germain Gillet, Philippe Gonzalo, Ruth Rimokh, and Marc Billaud

Précis: This important study raises concerns about using mTORC1 inhibitors for clinical management of cancer, given that they not only impair tumor immunity but also even promote EMT in epithelial cells, perhaps explaining the progressive pulmonary fibrosis associated with therapeutic use of mTOR inhibitors.

- 6632 **Hallmarks of Aromatase Inhibitor Drug Resistance Revealed by Epigenetic Profiling in Breast Cancer**
Maurice P.H.M. Jansen, Theo Knijnenburg, Esther A. Reijm, Iris Simon, Ron Kerkhoven, Marjolein Droog, Arno Velds, Steven van Laere, Luc Dirix, Xanthippi Alexi, John A. Foekens, Lodewyk Wessels, Sabine C. Linn, Els M.J.J. Berns, and Wilbert Zwart
Précis: Personalized breast cancer treatment might be achieved within the clinical setting by profiling DNA binding sites for transcription factors and epigenetic marks, suggesting that a similar strategy can be applied in other types of cancer.
- 6642 **The Transcription Factor IRF8 Counteracts BCR-ABL to Rescue Dendritic Cell Development in Chronic Myelogenous Leukemia**
Tomoya Watanabe, Chie Hotta, Shin-ichi Koizumi, Kazuho Miyashita, Jun Nakabayashi, Daisuke Kurotaki, Go R. Sato, Michio Yamamoto, Masatoshi Nakazawa, Hiroyuki Fujita, Rika Sakai, Shin Fujisawa, Akira Nishiyama, Zenro Ikezawa, Michiko Aihara, Yoshiaki Ishigatsubo, and Tomohiko Tamura
Précis: These findings suggest that the transcription factor IRF8 may offer an attractive target for the development of next-generation therapies for chronic myeloid leukemia.
- 6654 **Intestinal GUCY2C Prevents TGF- β Secretion Coordinating Desmoplasia and Hyperproliferation in Colorectal Cancer**
Ahmara V. Gibbons, Jieru E. Lin, Gilbert W. Kim, Glen P. Marszalowicz, Peng Li, Brian A. Stoecker, Erik S. Blomain, Satish Rattan, Adam E. Snook, Stephanie Schulz, and Scott A. Waldman
Précis: A tumor suppressor that coordinates EMT homeostasis acts in part through paracrine circuits that oppose tumor desmoplasia and progression.
- 6667 **CIP2A Modulates Cell-Cycle Progression in Human Cancer Cells by Regulating the Stability and Activity of PIK1**
Jae-Sung Kim, Eun Ju Kim, Jeong Su Oh, In-Chul Park, and Sang-Gu Hwang
Précis: These results establish a new function for an oncogenic inhibitor of the protein phosphatase PP2A in facilitating the stability of a critical mitotic kinase for cell cycle transit and tumorigenesis.
- 6679 **Loss of TBK1 Induces Epithelial-Mesenchymal Transition in the Breast Cancer Cells by ER α Downregulation**
Kyung-Min Yang, YunShin Jung, Jeong-Mi Lee, WonJoo Kim, Jin Ki Cho, Joon Jeong, and Seong-Jin Kim
Précis: A new regulator of estrogen receptor- α expression in breast cancer influences EMT, with prognostic and therapeutic relevance.
- 6690 **Maintenance of Androgen Receptor Inactivation by S-Nitrosylation**
Yu Qin, Anindya Dey, Hamsa Thayelee Purayil, and Yehia Daaka
Précis: This article reveals a new regulatory mechanism for the androgen receptor in prostate cancer, with immediate prospects for sequential targeting of its different domains to extend therapeutic efficacy in patients with advanced disease.
- 6700 **Cytoplasmic Irradiation Results in Mitochondrial Dysfunction and DRP1-Dependent Mitochondrial Fission**
Bo Zhang, Mercy M. Davidson, Hongning Zhou, Chunxin Wang, Winsome F. Walker, and Tom K. Hei
Précis: This study offers a mechanistic explanation for how ionizing radiation causes genotoxic damage, helping address long-standing gaps in knowledge concerning its extranuclear effects.
- 6711 **CD95L Cell Surface Cleavage Triggers a Prometastatic Signaling Pathway in Triple-Negative Breast Cancer**
Marine Malleter, Sébastien Tauzin, Alban Bessedé, Rémy Castellano, Armelle Goubard, Florence Godey, Jean Levêque, Pascal Jézéquel, Loïc Campion, Mario Campone, Thomas Ducret, Gaëtan MacGrogan, Laure Debure, Yves Collette, Pierre Vacher, and Patrick Legembre
Précis: These findings elucidate the mechanistic basis for a metastatic function of CD95L that is connected to cell migration, opening a new direction in understanding its contributions to carcinogenesis.
- 6722 **CDK1 Phosphorylation of YAP Promotes Mitotic Defects and Cell Motility and Is Essential for Neoplastic Transformation**
Shuping Yang, Lin Zhang, Miao Liu, Rong Chong, Shi-Jian Ding, Yuanhong Chen, and Jixin Dong
Précis: These results show how a pivotal effector of the Hippo pathway mediates its mitotic effects critical for oncogenesis.

6734 **Personalizing the Treatment of Pediatric Medulloblastoma: Polo-like Kinase 1 as a Molecular Target in High-Risk Children**

Joanna Triscott, Cathy Lee, Colleen Foster, Branavan Manoranjan, Mary Rose Pambid, Rachel Berns, Abbas Fotovati, Chitra Venugopal, Katrina O'Halloran, Aru Narendran, Cynthia Hawkins, Vijay Ramaswamy, Eric Bouffet, Michael D. Taylor, Ash Singhal, Juliette Hukin, Rod Rassekh, Stephen Yip, Paul Northcott, Sheila K. Singh, Christopher Dunham, and Sandra E. Dunn

Précis: These findings suggest repositioning inhibitors of a critical mitotic kinase, currently in clinical testing, to treat a deadly pediatric tumor.

6745 **Crizotinib Inhibits Metabolic Inactivation of Gemcitabine in c-Met–driven Pancreatic Carcinoma**

Amir Avan, Viola Caretti, Nicola Funel, Elena Galvani, Mina Maftouh, Richard J. Honeywell, Tonny Lagerweij, Olaf Van Tellingen, Daniela Campani, Dieter Fuchs, Henk M. Verheul, Gerrit-Jan Schuurhuis, Ugo Boggi, Godefridus J. Peters, Thomas Würdinger, and Elisa Giovannetti

Précis: A new set of imageable orthotopic models of human pancreatic cancer, which better recapitulates the tumors of origin, points to c-Met as a key therapeutic target for clinical evaluation in this disease.

6757 **Chk1 Targeting Reactivates PP2A Tumor Suppressor Activity in Cancer Cells**

Anchit Khanna, Otto Kauko, Camilla Böckelman, Anni Laine, Ilona Schreck, Johanna I. Partanen, Agnieszka Szwajda, Stefanie Bormann, Turker Bilgen, Merja Helenius, Yuba R. Pokharel, John Pimanda, Mike R. Russel, Caj Haglund, Kristina A. Cole, Juha Klefström, Tero Aittokallio, Carsten Weiss, Ari Ristimäki, Tapio Visakorpi, and Jukka Westermarck

Précis: These findings provide explanative power for single-agent antitumor activity of a new generation of Chk1 inhibitors that mediate blockade of MYC and survival in cancer cells.

6770 **Cetuximab Response of Lung Cancer–Derived EGF Receptor Mutants Is Associated with Asymmetric Dimerization**

Jeonghee Cho, Liang Chen, Naveen Sangji, Takafumi Okabe, Kimio Yonesaka, Joshua M. Francis, Richard J. Flavin, William Johnson, Jihyun Kwon, Soyoung Yu, Heidi Greulich, Bruce E. Johnson, Michael J. Eck, Pasi A. Jänne, Kwok-Kin Wong, and Matthew Meyerson

Précis: These findings reveal a likely mechanism for understanding how tumor cell growth is blocked by the EGF receptor antagonist cetuximab, used widely to treat epithelial cancers.

6780 **Taccalonolide Binding to Tubulin Imparts Microtubule Stability and Potent In Vivo Activity**

A.L. Risinger, J. Li, M.J. Bennett, C.C. Rohena, J. Peng, D.C. Schriemer, and S.L. Mooberry

Précis: The antitumor efficacy of a class of small molecules that stabilize microtubules by a novel mechanism provides a strong impetus to more fully explore the therapeutic potential of the binding site these molecules target on tubulin.

6793 **Small-Molecule Intramimics of Formin Autoinhibition: A New Strategy to Target the Cytoskeletal Remodeling Machinery in Cancer Cells**



L. Leanne Lash, Bradley J. Wallar, Julie D. Turner, Steven M. Vroegop, Robert E. Kilkuskie, Susan M. Kitchen-Goosen, H. Eric Xu, and Arthur S. Alberts

Précis: This report from a highly innovative study offers preclinical proof of concept for a new paradigm to target the cytoskeletal remodeling machinery of cancer cells, a clinically validated target, as a general strategy to treat human cancers.

TUMOR AND STEM CELL BIOLOGY

6804 **Requirements for Aurora-A in Tissue Regeneration and Tumor Development in Adult Mammals**

Ignacio Pérez de Castro, Cristina Aguirre-Portolés, Gonzalo Fernández-Miranda, Marta Cañamero, Dale O. Cowley, Terry Van Dyke, and Marcos Malumbres

Précis: Genetic ablation of an important mitotic kinase sheds light on how its function influences normal and neoplastic growth, with implications for understanding how small molecule inhibitors of this kinase might be used clinically.

6816 **RNAi-Mediated Silencing of Myc Transcription Inhibits Stem-like Cell Maintenance and Tumorigenicity in Prostate Cancer**

Gianluca Civenni, Anastasia Malek, Domenico Albino, Ramon Garcia-Escudero, Sara Napoli, Stefano Di Marco, Sandra Pinton, Manuela Sarti, Giuseppina M. Carbone, and Carlo V. Catapano

Précis: This important study offers a preclinical proof of concept to target Myc function in cancer stem-like cells as a general strategy to attack most if not all human cancers.

6828 **MyoD Is a Tumor Suppressor Gene in Medulloblastoma**

Joyoti Dey, Adrian M. Dubuc, Kyle D. Pedro, Derek Thirstrup, Brig Mecham, Paul A. Northcott, Xiaochong Wu, David Shih, Stephen J. Tapscott, Michael LeBlanc, Michael D. Taylor, and James M. Olson

Précis: A central muscle differentiation factor is for the first time shown to be expressed during development of the cerebellum and to function there as a tumor suppressor.

RETRACTIONS

6838 **Retraction: p53 Regulates Cellular Resistance to Complement Lysis through Enhanced Expression of CD59**

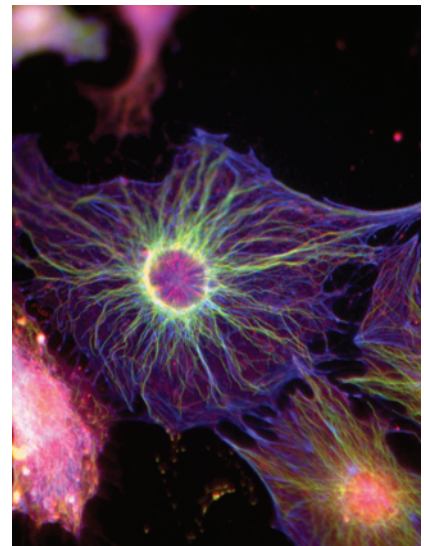
6839 **Retraction: Modulation of CD59 Expression by Restrictive Silencer Factor-Derived Peptides in Cancer Immunotherapy for Neuroblastoma**

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ABOUT THE COVER

Diaphanous-related formins create new and/or stabilize microfilament and microtubule structures that support polarized cell adhesion, migration, and division. GTP-bound Rho proteins activate these formins by direct binding. The molecular mechanism of Rho activation is through steric disruption of intramolecular interactions between Dia-inhibitory (DID) and Dia-autoregulatory (DAD) domains. Screening for compounds that block DID-DAD binding led to the discovery of intramimics, which are small molecules that interfere with autoinhibition, resulting in activation of cellular formins. Using immunofluorescence to detect deetyrosinated microtubules (a trait of stabilized microtubules), this image illustrates microtubules stabilized by intramimic exposure. For details on the mechanism and pharmacologic impairment of tumor growth, see article by Lash and colleagues on page 6793.



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