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-κB Nexus
Sudhanshu Shukla, Irene Rosita Pia Patric, Sivaarumugam Thinararjan, Sojaya Srinivasan, Baisakhi Mondal, Alangar S. Hegde, Bangalore A. Chandramouli, Vani Santosh, Arimappamagan Arivazhagan, and Kumaravel Somasundaram

6574 Parathyroid Hormone–Related Protein Drives a CD11b þ Gr1 þ 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. Daigualt, and Laurie K. McCauley

MOLECULAR AND CELLULAR PATHOBIOLOGY

6621 Genetic and Pharmacologic Inhibition of mTORC1 Promotes EMT by a TGF-β–Independent Mechanism
Ivan Mikaelian, Mohammad Malek, Rudy Gadi, Jean Viallet, Amandine Garcia, Anaïs Girard-Gagnepain, Cédric Hesling, Germain Gillet, Philippe Gonzalo, Ruth Rimokh, and Marc Billadea

6625 Soluble Carcinoembryonic Antigen Activates Endothelial Cells and Tumor Angiogenesis
Kira H. Bramswig, Marina Poettler, Matthias Unsell, Friedrich Wrha, 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.

6632 Adjuvants That Improve the Ratio of Antigen-Specific Effector to Regulatory T Cells Enhance Tumor Immunity
Rachel Perret, Sophie R. Sierr, Natalia K. Botelho, Stéphane Corgnac, 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.

6636 Enhancement of Antitumor Immunity in Lung Cancer by Targeting Myeloid-Derived Suppressor Cell Pathways
Anandi Sawant, Cara C. Schafer, Tong Huan Jin, Jaroslav 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.

MICROENVIRONMENT AND IMMUNOLOGY

6637 Genetic and Pharmacologic Inhibition of mTORC1 Promotes EMT by a TGF-β–Independent Mechanism
Ivan Mikaelian, Mohammad Malek, Rudy Gadi, Jean Viallet, Amandine Garcia, Anaïs Girard-Gagnepain, Cédric Hesling, Germain Gillet, Philippe Gonzalo, Ruth Rimokh, and Marc Billadea

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.

Contents
Hallmarks of Aromatase Inhibitor Drug Resistance Revealed by Epigenetic Profiling in Breast Cancer

 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.

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.

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.

CIP2A Modulates Cell-Cycle Progression in Human Cancer Cells by Regulating the Stability and Activity of Pkl
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.

Loss of TBK1 Induces Epithelial–Mesenchymal Transition in the Breast Cancer Cells by ERα 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.

Maintenance of Androgen Receptor Inactivation by S-Nitrosylation
Yu Qin, Anindya Dey, Hamisa Thayele 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.

Cytosplasmic 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.

CD95L Cell Surface Cleavage Triggers a Prometastatic Signaling Pathway in Triple-Negative Breast Cancer
Marine Malleter, Sébastien Tauzin, Alban Bessede, Rémy Castellano, Armelle Goubard, Florence Godey, Jean Levêque, Pascal Jézéquel, Loic 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.

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.
**THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY**

6734

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


**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, Niccola 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, Godfriedus J. Peters, Thomas Wurdinger, 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 Suppresser Activity in Cancer Cells**


**Précis:** These findings provide explanatory 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**


**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**


**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**


**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-Portoles, 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.
**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.

---

**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.

---

**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 detyrosinated 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.