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


Précis: This study identifies a global DNA methylation profile of glioblastoma tumors, revealing a potential therapeutic target.

MOLECULAR AND CELLULAR PATHOBIOLOGY

6621 Genetic and Pharmacologic Inhibition of mTORC1 Promotes EMT by a TGF-β–Independent Mechanism Ivan Mikaëlian, Mouhannad Malek, Rudy Gadel, Jean Viallet, Amandine Garcia, Anaïs Girard-Gagnepain, Cédric Hesling, Germaine Gillet, Philippe Gonzalo, Ruth Rimokh, and Marc Billard

Précis: This study reveals that inhibiting mTORC1 can promote epithelial-to-mesenchymal transition (EMT) in cancer, providing insights into the complex interplay between mTOR and EMT.

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, Jong Won Seo, Fabiana N. Soki, Sun Wook Cho, Stephanie D. Daignault, and Stephanie Corgnac

Précis: This study identifies a novel mechanism for prostate cancer progression involving parathyroid hormone-related protein (PTHrP) and immune cell interactions.
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 Plk1

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, Hamsa 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, Remy Castellano, Armelle Goubard, Florence Godey, Jean Levêque, Pascal Jézéquel, Loïc Cambon, 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.
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.

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.

Chk1 Targeting Reactivates PP2A Tumor Suppressor 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.

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.

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.

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.

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

Igacuo Pérez de Castro, Cristiana Aguirre-Portoles, Gonzalo Fernández-Miranda, Marta Cañamero, Dale O. Cowley, Terry Van Dyke, and Marcos Mahombres

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 García-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.

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**RETRACTIONS**

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

**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 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.

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