REVIEWS

2655 Releasing Pressure in Tumors: What Do We Know So Far and Where Do We Go from Here? A Review
Arizan B. Ariffin, Patrick F. Forde, Saleem Jahangeer, Declan M. Soden, and John Hinchion

2663 Chemotherapeutic Targeting of Cancer-Induced Immunosuppressive Cells
Darya Alizadeh and Nicolas Larmonier

PRIORITY REPORT

2669 BCR-ABL–Induced Deregulation of the IL-33/ST2 Pathway in CD34(+) Progenitors from Chronic Myeloid Leukemia Patients
Anaïs Levescot, Stéphane Flamant, Sara Basbous, Florence Jacomet, Olivier Féraud, Elvire Anne Bourgeois, Marie-Laure Bonnet, Christine Giraud, Lydia Roy, Anne Barra, Jean-Claude Chomel, Ali Turhan, François Guilhot, Jean-Philippe Girard, Jean-Marc Gombert, and André Herbelin
Précis: These findings support a role for the IL-33/ST2 alarmin pathway in CML maintenance and therapeutic resistance, suggesting a tractable route to degrade resistance and extend survival in relapsed patients.

CLINICAL STUDIES

2677 CHD7 Expression Predicts Survival Outcomes in Patients with Resected Pancreatic Cancer
Précis: A rationale-driven strategy and drug sensitivity screen identified a novel candidate biomarker that may be clinically useful to better individualize treatment of patients with pancreatic cancer.

INTEGRATED SYSTEMS AND TECHNOLOGIES

2688 Distinguishing between Benign and Malignant Melanocytic Nevi by In Vivo Multiphoton Microscopy
Mihaela Balu, Kristen M. Kelly, Christopher B. Zachary, Ronald M. Harris, Tatiana B. Krasieva, Karsten König, Anthony J. Durkin, and Bruce J. Tromberg
Précis: This study describes a method to reduce the need for biopsies and to improve the accuracy of diagnosis in the early detection of melanoma, a clinical imperative in preventing disease progression.

MICROENVIRONMENT AND IMMUNOLOGY

2698 Cancer Stem-like Cells Derived from Chemoresistant Tumors Have a Unique Capacity to Prime Tumorigenic Myeloid Cells
Tsunaki Yamashina, Muhammad Baghdadi, Akihiro Yoneda, Ichiro Kinoshita, Shinya Suzu, Hirotoshi Dosaka-Akita, and Masahisa Jinushi
Précis: This study reveals an unexpected ability of cancer stem-like cells in supporting the generation of immunosuppressive myeloid cells linked to anticancer drug resistance.

2710 Elimination of IL-10–Inducing T-Helper Epitopes from an IGFBP-2 Vaccine Ensures Potent Antitumor Activity
Denise L. Cecil, Gregory E. Holt, Kyong Hwa Park, Ekram Gad, Lauren Rastetter, Jennifer Childs, Doreen Higgins, and Mary L. Disis
Précis: Selection of particular portions of a tumor antigen that can stimulate T cells without generating immunosuppressive responses provides a capability to design vaccines displaying a more effective antitumor response.

MOLECULAR AND CELLULAR PATHOBIOLOGY

2719 Human Rhomboid Family-1 Suppresses Oxygen-Independent Degradation of Hypoxia-Inducible Factor-1α in Breast Cancer
Zhuan Zhou, Fangfang Liu, Zhi-Song Zhang, Feifei Shu, Yangyang Zheng, Li Fu, and Lu-Yuan Li
Précis: A nonprotease related to a class of intramembrane proteases (rhomboid proteases) is found to control HIF1α degradation in an oxygen-independent manner, greatly expanding knowledge about how this core regulator of aggressive solid tumors is controlled.
Tumor Endothelial Markers Define Novel Subsets of Cancer-Specific Circulating Endothelial Cells Associated with Antitumor Efficacy

Reza Mehran, Monique Nilsson, Mehrdad Khajavi, Zhijiang Du, Tina Caxcone, Hua Kang Wu, Andrea Cortes, Li Xu, Amado Zurita, Robert Schier, Bernhard Riedel, Randa El-Zein, and John V. Heymach

Précis: This report describes a blood-based surrogate marker to assess the presence of tumor vasculature and antiangiogenic drug activity.

Biallelic DICER1 Mutations in Sporadic Pleuropulmonary Blastoma

Masafumi Seki, Kenichi Yoshida, Yuichi Shiraishi, Teppei Shimamura, Yusuke Sato, Riki Nishimura, Yusuke Okuno, Kenichi Chiba, Hiroko Tanaka, Keisuke Kato, Motohiro Kato, Roji Hanada, Yuko Nomura, Myoung-Ja Park, Toshiaki Ishida, Akira Oka, Takashi Igarashi, Satoru Miyano, Yasuhide Hayashi, Seishi Ogawa, and Junko Takita

Précis: A rare pediatric tumor with poorly understood pathogenesis is found to be characterized by nearly universal biallelic mutations in the microRNA processing enzyme DICER1, with an obligatory somatic RNase IIIb domain mutation, along with less frequent but still common mutations in p53.

HNRNPAB Induces Epithelial–Mesenchymal Transition and Promotes Metastasis of Hepatocellular Carcinoma by Transcriptionally Activating SNAIL

Zheng-Jun Zhou, Zhi Dai, Shao-Lai Zhou, Zhi-Qiang Hu, Qing Chen, Yi-Ming Zhao, Ying-Hong Shi, Qiang Gao, Wei-Zhong Wu, Shuang-Jian Qiu, Jian Zhou, and Jia Fan

Précis: Overexpression of a ribonuclear protein that transcriptionally activates the EMT regulator Snail confers metastatic properties and poor prognosis in liver cancer, a pathway that may have broader relevance in human cancer.

NF-κB Gene Signature Predicts Prostate Cancer Progression

Renjie Jin, Yajun Yi, Fiona E. Yull, Timothy S. Blackwell, Peter E. Clark, Tatsuki Koyama, Joseph A. Smith Jr, and Robert J. Matusik

Précis: An expression signature generated in an NF-κB-activated mouse model of prostatic hyperplasia successfully predicts disease-specific survival and distant metastasis-free survival in prostate cancer patients.

BRC1 Deficiency Exacerbates Estrogen-Induced DNA Damage and Genomic Instability


Précis: This study provides pivotal new insights into the long-standing question of why BRCA1 mutation drives the formation of estrogen-regulated tissues, despite the general role of BRCA1 in DNA repair in all cell types, with implications for how to prevent breast cancer in BRCA1 carriers.

CLPTM1L Promotes Growth and Enhances Aneuploidy in Pancreatic Cancer Cells


Précis: A gene that lies at human chromosome 5p15.33 and harbors germline risk variants for multiple cancers is a plausible candidate for an important pancreatic cancer susceptibility allele.

PREVENTION AND EPIDEMIOLOGY

Emergence, Involution, and Progression to Carcinoma of Mutant Clones in Normal Endometrial Tissues

George L. Mutter, Nicolas M. Monte, Donna Neuberg, Alex Ferenczy, and Charis Eng

Précis: These findings show that the prevalence and turnover rate of latent endometrial precancers is high over time in otherwise normal-appearing tissues, with implications for understanding cancer etiology.
THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

2803 Sphingosine Kinase 2 Promotes Acute Lymphoblastic Leukemia by Enhancing MYC Expression
Craig T. Wallington-Beddoe, Jason A. Powell, Daochen Tong, Stuart M. Pitson, Kenneth F. Bradstock, and Linda J. Bendall

Précis: This study offers a tractable approach to target MYC expression in human cancer where it may be a universal therapeutic target, addressing the long-standing but mainly intractable problem of how to selectively block MYC function in the disease setting.

2816 Transient Antiangiogenic Treatment Improves Delivery of Cytotoxic Compounds and Therapeutic Outcome in Lung Cancer
Sampurna Chatterjee, Caroline Wieczorek, Jakob Schottle, Maike Siobal, Yvonne Hinze, Thomas Franz, Alexandra Florin, Joanna Adamczak, Lukas C. Heukamp, Bernd Neumaier, and Roland T. Ullrich

Précis: These findings offer compelling preclinical evidence that short-term antiangiogenic therapy can promote a transient normalization of tumor vessels that improves the delivery and efficacy of cytotoxic drugs, with clinical implications for how to properly schedule the most effective use of antiangiogenic drugs in patients.

2825 EGFR-Mediated Chromatin Condensation Protects KRAS-Mutant Cancer Cells against Ionizing Radiation
Meng Wang, Ashley M. Kern, Marieke Huiskötter, Patricia Greninger, Anurag Singh, Yunfeng Pan, Dipanjan Chowdhury, Mechthild Krause, Michael Baumann, Cyril H. Benes, Jason A. Efstathiou, Jeff Settleman, and Henning Willers

Précis: These findings challenge a paradigm for understanding the resistance of KRAS-mutant cancers to EGFR inhibitors, with implications for treating lung cancer in particular.

2835 ATR Pathway Inhibition Is Synthetically Lethal in Cancer Cells with ERCC1 Deficiency
Karen B. Mohri, Gina M. Kavanaugh, and David Cortez

Précis: Drugs that target the ATR pathway of DNA damage repair may offer particular utility in cancers with reduced ATR pathway function or reduced levels of ERCC4 activity, with implications for treatment of a broad array of aggressive tumors such as triple-negative breast cancers and lung cancers.

2846 Rapamycin Rescues ABT-737 Efficacy in Small Cell Lung Cancer
Eric E. Gardner, Nick Connis, John T. Poirier, Leslie Cope, Irina Dobromilskaya, Gary L. Gallia, Charles M. Rudin, and Christine L. Hann

Précis: This work provides support for rational combination therapy with mTOR and Bcl-2 inhibitors for the treatment of small-cell lung cancer.

TUMOR AND STEM CELL BIOLOGY

2857 Differential Effects of RUNX2 on the Androgen Receptor in Prostate Cancer: Synergistic Stimulation of a Gene Set Exemplified by SNAI2 and Subsequent Invasiveness
Gillian H. Little, Sanjeev K. Baniwal, Helty Adisetiyono, Susan Groshen, Nyam-Osor Chimge, Sun Young Kim, Omar Khalid, Debra Hawes, Jeremy O. Jones, Jacek Pinski, Dustin E. Schones, and Baruch Frenkel

Précis: A prostate cancer-associated transcription factor known to inhibit androgen-dependent gene expression was found to activate certain genes that drive invasion, with implications for prognosis and individualized therapy.

2869 Endothelial Cell-Secreted EGF Induces Epithelial to Mesenchymal Transition and Endows Head and Neck Cancer Cells with Stem-like Phenotype
Zhaocheng Zhang, Zhihong Dong, Isabel S. Lauxen, Manoel Sant’Ana Filho, and Jacques E. Nor

Précis: These findings suggest that vascular endothelial cells contribute to dissemination of carcinomas by secreting factors that endow carcinoma cells with enhanced motility and stemness.

2882 KLF5 Regulates the Integrity and Oncogenicity of Intestinal Stem Cells
Takeo Nakaya, Seishi Ogawa, Ichiro Manabe, Masami Tanaka, Masashi Sanada, Toshiro Sato, Makoto M. Takeo, Kazuki Nakao, Hans Clevers, Masashi Fukayama, Masahiko Kuroda, and Ryozo Nagai

Précis: This study offers a genetic proof of concept in the mouse that the stem cell integrity gene KLF5 acts as a core regulator of intestinal oncogenesis at the stem cell level, and it further suggests KLF5 targeting may offer a therapeutic strategy to eradicate stem-like cells in colorectal cancer.
A Meta-analysis of Lung Cancer Gene Expression Identifies PTK7 as a Survival Gene in Lung Adenocarcinoma
Ron Chen, Purvesh Khatri, Pawel K. Mazur, Melanie Polin, Yanyan Zheng, Dedeptra Vaka, Chuong D. Hoang, Joseph Shrago, Yue Xu, Silvestre Vicent, Atul J. Butte, and E. Alejandro Sweet-Cordero

Précis: These findings define a little-studied protein tyrosine kinase as a highly and specifically expressed gene and a potential therapeutic target in lung adenocarcinoma.

LETTER TO THE EDITOR

Lipid Metabolism Signatures in NASH-Associated HCC—Letter
Sonja M. Kessler, Stephan Laggai, Ahmad Barghash, Volkhard Helms, and Alexandra K. Kiemer

ABOUT THE COVER

The BH3 mimetics ABT-737/263 were developed to trigger programmed cell death (apoptosis) in tumors that express high levels of the antiapoptotic proteins BCL-2 and BCL-xL. Promising preclinical data in chronic lymphocytic leukemia (CLL) and small cell lung cancer (SCLC) warranted clinical investigation; however, single agent responses to ABT-263 in extensive-stage SCLC were minimal. Here, using patient-derived xenograft (PDX) models of SCLC, it was found that responses to single agent ABT-737 were acute in duration and accompanied by decreases in HIF-1α target genes. Using transcriptome signatures of ABT-737 responses, the authors identified that classes of PI3K/mTOR inhibitors were synergistic when combined with BH3 mimetics in vitro and provided durable tumor regressions in BCL-2-expressing PDX models of SCLC in vivo. Interestingly, the mTOR inhibitor rapamycin preserved levels of BAX protein, a requisite gateway for programmed cell death by ABT-737. These data add a new light on acute resistance mechanisms targeting antiapoptotic proteins. For details, see article by Gardner and colleagues on page 2846.