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- 834 **Decitabine Induces Gene Derepression on Monosomic Chromosomes: *In Vitro* and *In Vivo* Effects in Adverse-Risk Cytogenetics AML**  
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These findings unravel the molecular mechanism underlying the intriguing clinical activity of HMAs in AML/MDS patients with chromosome 7 deletions and other monosomal karyotypes.  
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- 847 **3D Functional Genomics Screens Identify CREBBP as a Targetable Driver in Aggressive Triple-Negative Breast Cancer**  
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This study demonstrates that CREBBP genomic alterations drive aggressive TNBC, lung cancer, and lymphomas and may be selectively treated with clinical CDK4/6 inhibitors.

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## METABOLISM AND CHEMICAL BIOLOGY

**860 Targeting p300/CBP Attenuates Hepatocellular Carcinoma Progression through Epigenetic Regulation of Metabolism**

Ling-Yan Cai, Shi-Jie Chen, Sen-Hao Xiao, Qin-Juan Sun, Chen-Hong Ding, Bai-Nan Zheng, Xin-Yan Zhu, Shu-Qing Liu, Feng Yang, Ya-Xi Yang, Bing Zhou, Cheng Luo, Xin Zhang, and Wei-Fen Xie

This study demonstrates p300/CBP as a critical epigenetic regulator of glycolysis-related metabolic enzymes in HCC and identifies the p300/CBP inhibitor B029-2 as a potential therapeutic strategy in this disease.

**873 Combinatorial Normalization of Liver-Derived Cytokine Pathways Alleviates Hepatic Tumor-Associated Cachexia in Zebrafish**

Fei Fei, Shaoyang Sun, Qiang Li, Zhou Pei, Lei Wang, Ranran Zhang, Feihong Luo, Min Yu, and Xu Wang

Disruption of leptin signaling with normalized Igf1 expression significantly rescues anorexia, muscle wasting, and adipose wasting in Ras- and Myc-driven zebrafish models of HCC.

## MOLECULAR CELL BIOLOGY

**885 Cancer-Induced Muscle Wasting Requires p38 $\beta$  MAPK Activation of p300**

Thomas K. Sin, Guohua Zhang, Zicheng Zhang, James Z. Zhu, Yan Zuo, Jeffrey A. Frost, Min Li, and Yi-Ping Li

These findings demonstrate that prevention of p38 $\beta$  MAPK-mediated activation of p300 by the FDA-approved kinase inhibitor, nilotinib, ameliorates cancer cachexia, representing a potential therapeutic strategy against this syndrome.

**898 MDMX Recruits Ubch5c to Facilitate MDM2 E3 Ligase Activity and Subsequent p53 Degradation *In Vivo***

Jing Yang, Aiwen Jin, Jing Han, Xin Chen, Junnian Zheng, and Yanping Zhang

This study provides the first *in vivo* evidence of MDMX facilitating MDM2-mediated p53 degradation, clarifying its role in the regulation of this critical tumor suppressor.

**910 A GRN Autocrine-Dependent FAM135B/AKT/mTOR Feedforward Loop Promotes Esophageal Squamous Cell Carcinoma Progression**

Dezuo Dong, Weimin Zhang, Wenchang Xiao, Qingnan Wu, Yiren Cao, Xiaohan Gao, Lijie Huang, Yan Wang, Jie Chen, Weihu Wang, and Qimin Zhan

These findings investigate the mechanisms of FAM135B in promoting ESCC progression and suggest new potential prognostic biomarkers and therapeutic targets in patients with ESCC.

**923 DMDRMR-Mediated Regulation of m<sup>6</sup>A-Modified CDK4 by m<sup>6</sup>A Reader IGF2BP3 Drives ccRCC Progression**

Yinmin Gu, Shaoxi Niu, Yang Wang, Liqiang Duan, Yongbo Pan, Zhou Tong, Xu Zhang, Zhenyu Yang, Bo Peng, Xiaodong Wang, Xiaoqi Han, Yuxin Li, Tianyou Cheng, Yajuan Liu, Lina Shang, Tongfeng Liu, Xiwang Yang, Minxuan Sun, Siyuan Jiang, Chang Zhang, Ning Zhang, Qinong Ye, and Shan Gao

This study demonstrates that the lncRNA *DMDRMR* acts as a cofactor for IGF2BP3 to stabilize target genes in an m<sup>6</sup>A-dependent manner, thus exerting essential oncogenic roles in ccRCC.

**935 Robust p53 Stabilization Is Dispensable for Its Activation and Tumor Suppressor Function**

Ning Kon, Michael Churchill, Huan Li, Siddhartha Mukherjee, James J. Manfredi, and Wei Gu

Although robust p53 stabilization is critical for acute p53 responses such as DNA damage, this study underscores the important role of low basal p53 protein levels in p53 activation and tumor suppression.

**945 GSK3 $\beta$ -Mediated Expression of CUG-Translated WT1 Is Critical for Tumor Progression**

Hisae Yoshitomi, Kun Y. Lee, Ke Yao, Seung Ho Shin, Tianshun Zhang, Qiushi Wang, Souren Paul, Eunmiri Roh, Joohyun Ryu, Hanyong Chen, Faisal Aziz, Abhijit Chakraborty, Ann M. Bode, and Zigang Dong

These findings demonstrate that CUG-translated WT1 plays an oncogenic role *in vivo*, and GSK3 $\beta$ -mediated phosphorylation of cugWT1 induces its ubiquitination and degradation in concert with FBXW8.

## TUMOR BIOLOGY AND IMMUNOLOGY

**956 Targeting MARCO and IL37R on Immunosuppressive Macrophages in Lung Cancer Blocks Regulatory T Cells and Supports Cytotoxic Lymphocyte Function**

Linnéa La Fleur, Johan Botling, Fei He, Catarina Pelicano, Chikai Zhou, Chenfei He, Giorgia Palano, Artur Mezheyeuski, Patrick Micke, Jeffrey V. Ravetch, Mikael C. I. Karlsson, and Dhifaf Sarhan

This study defines tumor-derived IL37 and the macrophage scavenger receptor MARCO as potential therapeutic targets to remodel the immune-suppressive microenvironment in patients with lung cancer.

**968 Pharmacologic Activation of LXR Alters the Expression Profile of Tumor-Associated Macrophages and the Abundance of Regulatory T Cells in the Tumor Microenvironment**

José M. Carbó, Theresa E. León, Joan Font-Díaz, Juan Vladimir De la Rosa, Antonio Castrillo, Felix R. Picard, Daniel Staudenraus, Magdalena Huber, Lidia Cedó, Joan Carles Escolà-Gil, Lucía Campos, Latifa Bakiri, Erwin F. Wagner, Carme Caelles, Thomas Stratmann, Jo A. Van Genderachter, and Annabel F. Valledor

This study reveals unrecognized roles of LXR in the transcriptional control of the tumor microenvironment and suggests use of a synthetic LXR agonist as a novel therapeutic strategy to stimulate antitumor activity.

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- 986 ORAI2 Promotes Gastric Cancer Tumorigenicity and Metastasis through PI3K/Akt Signaling and MAPK-Dependent Focal Adhesion Disassembly**  
Shayi Wu, Miao Chen, Jiao Huang, Feifei Zhang, Zhaojie Lv, Yongxu Jia, Yu-Zhu Cui, Liang-Zhan Sun, Ying Wang, Ying Tang, Krista R. Verhoeft, Yan Li, Yanru Qin, Xiang Lin, Xin-Yuan Guan, and Ka-On Lam  
These findings describe the critical role of ORAI2 in gastric cancer cell migration and tumor metastasis and uncover the translational potential to advance drug discovery along the ORAI2 signaling pathway.
- 1001 Newly Identified Members of FGFR1 Splice Variants Engage in Cross-talk with AXL/AKT Axis in Salivary Adenoid Cystic Carcinoma**  
Joseph O. Humtsoe, Hyun-Su Kim, Brandon Leonard, Shizhang Ling, Bhumsuk Keam, Luigi Marchionni, Bahman Afsari, Michael Considine, Alexander V. Favorov, Elana J. Fertig, Hyunseok Kang, and Patrick K. Ha  
This study identifies several FGFR1 variants that function through the AXL/AKT signaling pathway independent of FGF/FGFR1, desensitizing cells to FGFR1 inhibitor suggestive of a potential resistance mechanism in ACC.
- 1014 Therapeutic Targeting of Metadherin Suppresses Colorectal and Lung Cancer Progression and Metastasis**  
Minhong Shen, Shanshan Xie, Michelle Rowicki, Sven Michel, Yong Wei, Xiang Hang, Liling Wan, Xin Lu, Min Yuan, John F. Jin, Frank Jaschinski, Tianhua Zhou, Richard Klar, and Yibin Kang  
This study provides new insights into the mechanism of MTDH in promoting colorectal and lung cancers, as well as genetic and pharmacologic evidence supporting the development of MTDH-targeting therapeutics.
- 1026 KIF15-Mediated Stabilization of AR and AR-V7 Contributes to Enzalutamide Resistance in Prostate Cancer**  
Lin Gao, Wenbo Zhang, Jing Zhang, Junmei Liu, Feifei Sun, Hui Liu, Jing Hu, Xin Wang, Xueli Wang, Peng Su, Shouzhen Chen, Sifeng Qu, Benkang Shi, Xueting Xiong, Weiwen Chen, Xuesen Dong, and Bo Han  
These findings demonstrate how reciprocal activation between KIF15 and AR contributes to enzalutamide resistance in prostate cancer and highlight cotargeting KIF15 and AR as a therapeutic strategy for these tumors.
- 1040 Cancer Cell Fitness Is Dynamic**  
Luana S. Lenz, Juliano L. Faccioni, Paula A. Bracco, Jephesson A.F. Santos, Luiza C. Pereira, Julieti H. Buss, Mauricio T. Tamborindeguy, Daphne Torgo, Thayana Monteiro, Giovana B. Mantovani, Carolina N. Santo, Julia C. Marcolin, Eloisa Dalsin, Alvaro Vigo, Sidia M. Callegari-Jacques, Andrew O. Silva, Giovana R. Onzi, Karine R. Begnini, and Guido Lenz  
Cancer cell fitness is dynamic over the course of the formation of colonies. This dynamic behavior is mediated by asymmetric mitosis, ERK activity, cell-cycle duration, and DNA repair capacity in the absence or presence of a drug.
- TRANSLATIONAL SCIENCE**
- 1052 E7386, a Selective Inhibitor of the Interaction between  $\beta$ -Catenin and CBP, Exerts Antitumor Activity in Tumor Models with Activated Canonical Wnt Signaling**  
**A C**  
Kazuhiko Yamada, Yusaku Hori, Satoshi Inoue, Yuji Yamamoto, Kentaro Iso, Hiroshi Kamiyama, Atsumi Yamaguchi, Takayuki Kimura, Mai Uesugi, Junichi Ito, Masahiro Matsuki, Kazutaka Nakamoto, Hitoshi Harada, Naoki Yoneda, Atsushi Takemura, Ikuo Kushida, Naomi Wakayama, Kenji Kubara, Yu Kato, Taro Semba, Akira Yokoi, Masayuki Matsukura, Takenao Odagami, Masao Iwata, Akihiko Tsuruoka, Toshimitsu Uenaka, Junji Matsui, Tomohiro Matsushima, Kenichi Nomoto, Hiroyuki Kouji, Takashi Owa, Yasuhiro Funahashi, and Yoichi Ozawa  
These findings demonstrate that the novel anticancer agent E7386, modulates Wnt/ $\beta$ -catenin signaling, altering the tumor immune microenvironment and exhibiting synergistic antitumor activity in combination with anti-PD-1 antibody.
- 1063 ATG5-Dependent Autophagy Uncouples T-cell Proliferative and Effector Functions and Separates Graft-versus-Host Disease from Graft-versus-Leukemia**  
Katherine Oravec-Wilson, Corinne Rossi, Cynthia Zajac, Yaping Sun, Lu Li, Thomas Decoville, Hideaki Fujiwara, Stephanie Kim, Daniel Peltier, and Pavan Reddy  
These findings demonstrate that induction of autophagy in donor T-cell promotes GVHD, while inhibition of T-cell autophagy mitigates GVHD without substantial loss of GVL responses.
- 1076 A Very Long-Acting PARP Inhibitor Suppresses Cancer Cell Growth in DNA Repair-Deficient Tumor Models**  
Shaun D. Fontaine, Gary W. Ashley, Peter J. Houghton, Raushan T. Kurmasheva, Morgan Diolaiti, Alan Ashworth, Cody J. Peer, Ryan Nguyen, William D. Figg Sr., Denis R. Beckford-Vera, and Daniel V. Santi  
These findings demonstrate that a single injection of a long-acting prodrug of the PARP inhibitor talazoparib in murine xenografts provides tumor suppression equivalent to a month of daily dosing of talazoparib.
- 1087 JMJD6 Is a Druggable Oxygenase That Regulates AR-V7 Expression in Prostate Cancer**  
**A C**  
Alec Paschalis, Jonathan Welti, Antje J. Neeb, Wei Yuan, Ines Figueiredo, Rita Pereira, Ana Ferreira, Ruth Riisnaes, Daniel Nava Rodrigues, Juan M. Jiménez-Vacas, Soojin Kim, Takuma Uo, Patrizio Di Micco, Anthony Tumber, Md. Saiful Islam, Marc A. Moesser, Martine Abboud, Akane Kawamura, Bora Gurel, Rossitza Christova, Veronica S. Gil, Lorenzo Buroni, Mateus Crespo, Susana Miranda, Maryou B. Lambros, Suzanne Carreira, Nina Tunariu, Andrea Alimonti, SU2C/PCF International Prostate Cancer Dream Team, Bissan Al-Lazikani, Christopher J. Schofield, Stephen R. Plymate, Adam Sharp, and Johann S. de Bono  
This study identifies JMJD6 as being critical for the generation of AR-V7 in prostate cancer, where it may serve as a tractable target for therapeutic intervention.

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**1101 Identifying Clear Cell Renal Cell Carcinoma Coexpression Networks Associated with Opioid Signaling and Survival**

Joseph R. Scarpa, Renzo G. DiNatale, Roy Mano, Andrew W. Silagy, Fengshen Kuo, Takeshi Irie, Patrick J. McCormick, Gregory W. Fischer, A. Ari Hakimi, and Joshua S. Mincer

This study suggests a possible molecular mechanism for opioid effects on cancer outcomes generally, with implications for personalization of analgesic regimens.

**1111 MUC1-C Activates the BAF (mSWI/SNF) Complex in Prostate Cancer Stem Cells**

**AC**

Masayuki Hagiwara, Yota Yasumizu, Nami Yamashita, Hasan Rajabi, Atsushi Fushimi, Mark D. Long, Wei Li, Atrayee Bhattacharya, Rehan Ahmad, Mototsugu Oya, Song Liu, and Donald Kufe

These findings show that MUC1-C, which promotes prostate cancer progression, activates a novel pathway that drives the BAF remodeling complex, induces NOTCH1 and NANOG, and promotes self-renewal of prostate cancer stem cells.

## CONVERGENCE AND TECHNOLOGIES

**1123 Optimal Timing for Cancer Screening and Adaptive Surveillance Using Mathematical Modeling**

Kit Curtius, Anup Dewanji, William D. Hazelton, Joel H. Rubenstein, and Georg E. Luebeck

This study demonstrates how mathematical modeling of cancer evolution can be used to optimize screening regimes, with the added potential to improve surveillance regimes.

**1135 Turnover Modulates the Need for a Cost of Resistance in Adaptive Therapy**

Maximilian A.R. Strobl, Jeffrey West, Yannick Viossat, Mehdi Damaghi, Mark Robertson-Tessi, Joel S. Brown, Robert A. Gatenby, Philip K. Maini, and Alexander R.A. Anderson

Tumor cell turnover modulates the speed of selection against drug resistance by amplifying the effects of competition and resistance costs; as such, turnover is an important factor in resistance management via adaptive therapy.

See related commentary, p. 811

## POPULATION AND PREVENTION SCIENCE

**1148 Patterns of Human Leukocyte Antigen Class I and Class II Associations and Cancer**

Zhiwei Liu, Andriy Derkach, Kelly J. Yu, Meredith Yeager, Yu-Sun Chang, Chien-Jen Chen, Ulf Gyllensten, Qing Lan, Mei-Hsuan Lee, James D. McKay, Nathaniel Rothman, Hwai-I Yang, Allan Hildesheim, and Ruth M. Pfeiffer

GWAS of >71,000 individuals across 27 cancer types suggest that patterns of HLA Class I and Class II associations may provide etiologic insights for cancer.

**1153 Time-Dependent Effects of Oral Contraceptive Use on Breast, Ovarian, and Endometrial Cancers**

**AC**

Torgny Karlsson, Therese Johansson, Julia Höglund, Weronica E. Ek, and Åsa Johansson

These results enable women and physicians to make more informed decisions considering oral contraceptive use, thus constituting an important step towards personalized medicine.

**1163 Racial/Ethnic Disparities in All-Cause Mortality among Patients Diagnosed with Triple-Negative Breast Cancer**

Fei Wang, Wei Zheng, Christina E. Bailey, Ingrid A. Mayer, Jennifer A. Pietenpol, and Xiao-Ou Shu

These findings highlight the need for equal healthcare to mitigate the black-white disparity and for investigations of contributors beyond healthcare for lower mortality among Asians and Hispanics.

## RESOURCE REPORTS

**1171 Interactive Classification of Whole-Slide Imaging Data for Cancer Researchers**

Sanghoon Lee, Mohamed Amgad, Pooya Mobadersany, Matt McCormick, Brian P. Pollack, Habiba Elfandy, Hagar Hussein, David A. Gutman, and Lee A.D. Cooper

An interactive machine learning tool for analyzing digital pathology images enables cancer researchers to apply this tool to measure histologic patterns for clinical and basic science studies.

**1178 The FABRIC Cancer Portal: A Ranked Catalogue of Gene Selection in Tumors Over the Human Coding Genome**

Guy Kelman, Nadav Brandes, and Michal Linial

A new cancer portal quantifies and presents gene selection in tumor over the entire human coding genome across 33 cancer types and pan-cancer.

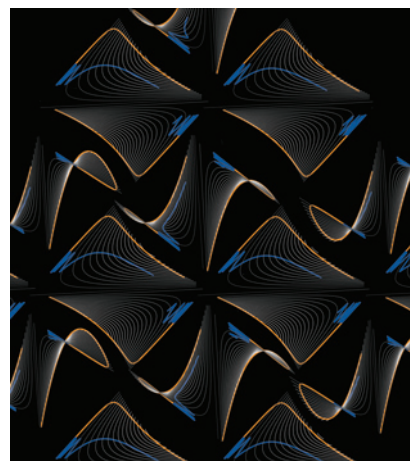
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## ABOUT THE COVER

Adaptive cancer therapy aims to delay cancer progression by exploiting competition between drug-sensitive and -resistant cells in the tumor. Drug dosing is adapted in a patient-specific fashion to maintain drug-sensitive cells that competitively suppress resistance (blue). This is in contrast to standard-of-care cancer treatment regimens that maximize cell kill and thereby cause the rapid competitive release of drug-resistant cells (orange). But, when will adaptive therapy work? Shown is a collage of so-called "phase plane" visualizations of a mathematical model with which the authors address this question. Each triangle represents a different parameterization. It was found that resource availability, resistance fraction, resistance cost, and cellular turnover integrate to modulate intratumoral competition. For details, see article by Strobl and colleagues on page 1135.



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