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These findings indicate that the osteosarcoma microenvironment composition is a major feature to identify hard-to-treat patient tumors at diagnosis and define the biological pathways and potential actionable targets associated with these tumors.

- 986** **Genome-Wide Association Analyses Identify *CATSPERE* as a Mediator of Colorectal Cancer Susceptibility and Progression**

Yixuan Meng, Mulong Du, Dongying Gu, Chen Li, Shuwei Li, Qiuyi Zhang, Shuai Ben, Qiuyuan Zhu, Junyi Xin, Zhengdong Zhang, Zhibin Hu, Hongbing Shen, Kewei Jiang, and Meilin Wang

A GWAS meta-analysis identifies a novel susceptibility locus harboring a genetic risk variant that mediates pleiotropic biological effects in colorectal tumorigenesis and progression.

METABOLISM AND CHEMICAL BIOLOGY

- 998** **Targeting Cellular Iron Homeostasis with Ionomycin in Diffuse Large B-cell Lymphoma**
Julie Devin, Tatiana Cañeque, Yea-Lih Lin, Lucie Mondoulet, Jean-Luc Veyrune, Matthieu Abouladze, Elvira Garcia De Paco, Ouissem Karmous Gadacha, Guillaume Cartron, Philippe Pasero, Caroline Bret, Raphaël Rodriguez, and Jerome Moreaux

Iron homeostasis represents a potential therapeutic target for high-risk patients with DLBCL that can be targeted with ionomycin to induce cell death and to sensitize tumor cells to conventional treatments.

MOLECULAR CELL BIOLOGY

- 1013** **Combined Inactivation of CTPS1 and ATR Is Synthetically Lethal to MYC-Overexpressing Cancer Cells**
Zhe Sun, Ziheng Zhang, Qiao-Qi Wang, and Ji-Long Liu
Inhibition of CTPS in MYC-overexpressing cells blocks pyrimidine synthesis while maintaining ribosome synthesis activity to create an anabolic imbalance that induces replication stress, providing a new approach to selectively target MYC-driven cancer.
See related commentary, p. 969

- 1025** **Identification of Active Bronchioalveolar Stem Cells as the Cell of Origin in Lung Adenocarcinoma**
Huijing Yin, Bo Jing, Dongliang Xu, Wenzheng Guo, Beibei Sun, Jie Zhang, Yueling Liao, Hongyong Song, Tong Wang, Shuli Liu, Yanbin Kuang, Min Hu, Kaimi Li, Siwei Zhang, Hongjia Zhang, Jianhua Xu, Xue Li, Jing Du, Yadi Wu, Yingli Wu, Qi Wang, Feng Yao, Y. Eugene Chin, Binhua P. Zhou, and Jiong Deng
Identification of active bronchioalveolar stem cells as lung adenocarcinoma cells of origin provides insights into mechanisms of lung tumorigenesis and could facilitate development of effective strategies for cancer prevention and therapy.
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1038 **Targeting LRRC15 Inhibits Metastatic Dissemination of Ovarian Cancer**

Upasana Ray, Deok-Beom Jung, Ling Jin, Yinan Xiao, Subramanyam Dasari, Sayantani Sarkar Bhattacharya, Prabhu Thirusangu, Julie K. Staub, Debarshi Roy, Bhaskar Roy, S. John Weroha, Xiaonan Hou, James W. Purcell, Jamie N. Bakkum-Gamez, Scott H. Kaufmann, Nagarajan Kannan, Anirban K. Mitra, and Viji Shridhar

This study identifies that LRRC15 activates β 1-integrin/FAK signaling to promote ovarian cancer metastasis and shows that the LRRC15-targeted antibody-drug conjugate ABBV-085 suppresses ovarian cancer metastasis in preclinical models.

1055 **CircRPN2 Inhibits Aerobic Glycolysis and Metastasis in Hepatocellular Carcinoma**

Jia Li, Zhi-Qiang Hu, Song-Yang Yu, Li Mao, Zheng-Jun Zhou, Peng-Cheng Wang, Yu Gong, Sheng Su, Jian Zhou, Jia Fan, Shao-Lai Zhou, and Xiao-Wu Huang

The circRNA circRPN2 is a potential prognostic biomarker and therapeutic target in hepatocellular carcinoma that suppresses aerobic glycolysis and metastasis.

TUMOR BIOLOGY AND IMMUNOLOGY

1070 **EBV Infection in Epithelial Malignancies Induces Resistance to Antitumor Natural Killer Cells via F3-Mediated Platelet Aggregation**

Xiaobing Duan, Haiwen Chen, Xiang Zhou, Pingjuan Liu, Xiao Zhang, Qian Zhu, Ling Zhong, Wanlin Zhang, Shanshan Zhang, Xinyu Zhang, Yanhong Chen, Yan Zhou, Chaopin Yang, Qisheng Feng, Yi-Xin Zeng, Miao Xu, and Tong Xiang

This study reveals a mechanism by which EBV-associated epithelial malignancies escape NK-cell-mediated immune surveillance, providing a new target for improving NK-cell immunotherapy.

1084 **Differential Kinase Activity Across Prostate Tumor Compartments Defines Sensitivity to Target Inhibition**

Nezihi Murat Karabacak, Yu Zheng, Taronish D. Dubash, Risa Burr, Douglas S. Micalizzi, Ben S. Wittner, Maoxuan Lin, Devon F. Wiley, Valentine Comaills, Erin Emmons, Kira L. Niederhoffer, Uyen Ho, Jacob Ukleja, Dante Che, Hannah Stowe, Linda T. Nieman, Wilhelm Haas, Shannon L. Stott, Michael S. Lawrence, David T. Ting, David T. Miyamoto, Daniel A. Haber, Mehmet Toner, and Shyamala Maheswaran

Single-cell mass cytometry analyses provide insights into the differences in kinase activity across tumor compartments and cell states, which contributes to heterogeneous responses to targeted therapies.

TRANSLATIONAL SCIENCE

1098 **Transient Inhibition of the JAK/STAT Pathway Prevents B-ALL Development in Genetically Predisposed Mice**

Ana Casado-García, Marta Isidro-Hernández, Ninad Oak, Andrea Mayado, Christine Mann-Ran, Javier Raboso-Gallego, Silvia Alemán-Arteaga, Alexandra Buhles, Dario Sterker, Elena G. Sánchez, Jorge Martínez-Cano, Oscar Blanco, Alberto Orfao, Diego Alonso-López, Javier De Las Rivas, Susana Riesco, Pablo Prieto-Matos, África González-Murillo, Francisco Javier García Criado, María Begoña García Cenador, Thomas Radimerski, Manuel Ramírez-Orellana, César Cobaleda, Jun J. Yang, Carolina Vicente-Dueñas, Andreas Weiss, Kim E. Nichols, and Isidro Sánchez-García

JAK/STAT inhibition suppresses tumorigenesis in a B-ALL-susceptible mouse model, presenting a novel approach to prevent B-ALL onset.

1110 **CIC-Mediated Modulation of MAPK Signaling Opposes Receptor Tyrosine Kinase Inhibitor Response in Kinase-Addicted Sarcoma**

Igor Odintsov, Michael V. Ortiz, Inna Khodos, Marissa S. Mattar, Allan J.W. Lui, Shinji Kohsaka, Elisa de Stanchina, Julia L. Glade Bender, Marc Ladanyi, and Romel Somwar

Novel models of kinase-rearranged sarcomas show that MAPK pathway feedback activation dampens responses to tyrosine kinase inhibitors, revealing the potential of combinatorial therapies to combat these tumors.

1128 **Development of Novel Aptamer-Based Targeted Chemotherapy for Bladder Cancer**

Yao Wang, Yang Zhang, Peng-Chao Li, Jiajie Guo, Fan Huo, Jintao Yang, Ru Jia, Juan Wang, Qiju Huang, Dan Theodorescu, Hanyang Yu, and Chao Yan

These findings identify a bladder cancer-specific aptamer that can be used for targeted delivery of chemotherapy, potentially reducing toxicity and enhancing therapeutic efficacy.

1140 **ATR Inhibitor AZD6738 (Ceralasertib) Exerts Antitumor Activity as a Monotherapy and in Combination with Chemotherapy and the PARP Inhibitor Olaparib**

Zena Wilson, Rajesh Odedra, Yann Wallez, Paul W.G. Wijnhoven, Adina M. Hughes, Joe Gerrard, Gemma N. Jones, Hannah Bargh-Dawson, Elaine Brown, Lucy A. Young, Mark J. O'Connor, and Alan Lau

This detailed preclinical investigation, including pharmacokinetics/pharmacodynamics and dose-schedule optimizations, of AZD6738/ceralasertib alone and in combination with chemotherapy or PARP inhibitors can inform ongoing clinical efforts to treat cancer with ATR inhibitors.

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CORRECTIONS

- 1153** **Correction: PHGDH Expression Is Required for Mitochondrial Redox Homeostasis, Breast Cancer Stem Cell Maintenance, and Lung Metastasis**
Debangshu Samanta, Youngrok Park, Shaida A. Andrabi, Laura M. Shelton, Daniele M. Gilkes, and Gregg L. Semenza

- 1154** **Correction: 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

ABOUT THE COVER

The image depicts the Battle of Chibi (meaning ‘Red Cliff’ in Chinese), one of the most famous battles in Chinese history. In the Battle of Chibi (208 AD), two groups joined forces to halt the advance of strong enemies. Similarly, Sun and colleagues target MYC-driven cancer with the combined inactivation of CTPS1 and ATR in this issue. The image depicts the two forces (in the shape of arrowheads) joining the battle (depicted by the fire). For details, see the article by Sun and colleagues on page 1013. (Concept, Ji-Long Liu; Illustration, Jia Du.)

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