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Modulation of the MDR phenotype has the potential to increase the efficacy of anticancer therapies. These findings show that the MDR transporter is a "double-edged sword" that can be turned against resistant cancer.

- 675 **A Feedback Circuitry between Polycomb Signaling and Fructose-1, 6-Bisphosphatase Enables Hepatic and Renal Tumorigenesis**

Kun Liao, Shuye Deng, Liyan Xu, Wenfeng Pan, Shiyu Yang, Fufu Zheng, Xingui Wu, Hongrong Hu, Zhijun Liu, Junhang Luo, Rui Zhang, Dong-Ming Kuang, Jiajun Dong, Yi Wu, Hui Zhang, Penghui Zhou, Jin-Xin Bei, Yang Xu, Yin Ji, Peng Wang, Huai-Qiang Ju, Rui-Hua Xu, and Bo Li

A novel feedback loop involving EZH2 and suppression of the gluconeogenesis enzyme FBPI promotes hepatocellular cancer growth.

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- 689 **Mass Spectrometry Imaging Enables Discrimination of Renal Oncocytoma from Renal Cell Cancer Subtypes and Normal Kidney Tissues**

Jialing Zhang, Shirley Q. Li, John Q. Lin, Wendong Yu, and Livia S. Eberlin

Metabolic data acquired by mass spectrometry imaging in conjunction with statistical modeling allows discrimination of renal tumors and has the potential to be used in the clinic to improve treatment of patients.

MOLECULAR CELL BIOLOGY

- 699 **Extracellular ATP and Purinergic P2Y₂ Receptor Signaling Promote Liver Tumorigenesis in Mice by Exacerbating DNA Damage**

Isabel Schullien, Birgit Hockenjos, Veerle van Marck, C. Korcan Ayata, Marie Follo, Robert Thimme, and Peter Hasselblatt

Extracellular ATP and subsequent P2Y₂ receptor function stimulate DNA damage responses and hepatocyte proliferation, thereby promoting hepatocarcinogenesis in mice. Targeting this pathway may be an attractive approach for chemoprevention of hepatocellular carcinoma.

- 709 **Cooperative Blockade of PKC α and JAK2 Drives Apoptosis in Glioblastoma**

Robyn A. Wong, Xujun Luo, Mimi Lu, Zhenyi An, Daphne A. Haas-Kogan, Joanna J. Phillips, Kevan M. Shokat, William A. Weiss, and Qi Wen Fan
These findings identify PKC α and JAK2 as targets that drive apoptosis in glioblastoma, potentially representing a clinically translatable approach for glioblastoma.

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Yongfeng Yang, Chuanzhen Yang, Tingting Li, Shuyu Yu, Tingting Gan, Jiazhi Hu, Jun Cui, and Xiaofeng Zheng
This study demonstrates that USP38 regulates genome stability and mediates cancer cell resistance to DNA-damaging therapy, providing insight into tumorigenesis and implicating USP38 as a potential target for cancer diagnosis.

TUMOR BIOLOGY AND IMMUNOLOGY

- 732** **HPV16 E5 Mediates Resistance to PD-L1 Blockade and Can Be Targeted with Rimantadine in Head and Neck Cancer**
Sayuri Miyauchi, P. Dominick Sanders, Kripa Guram, Sangwoo S. Kim, Francesca Paolini, Aldo Venuti, Ezra E.W. Cohen, J. Silvio Gutkind, Joseph A. Califano, and Andrew B. Sharabi
This study identifies a novel mechanism of resistance to anti-PD-1/PD-L1 immunotherapy mediated by HPV E5, which can be exploited using the HPV E5 inhibitor rimantadine to improve outcomes for head and neck cancer patients.
- 747** **Netrin-1 and Its Receptor DCC Are Causally Implicated in Melanoma Progression**
Amina Boussouar, Antonin Tortereau, Ambroise Manceau, Andrea Paradisi, Nicolas Gadot, Jonathan Vial, David Neves, Lionel Larue, Maxime Battistella, Christophe Leboeuf, Celeste Lebbé, Anne Janin, and Patrick Mehlen
Netrin-1 and its receptor DCC regulate melanoma progression, suggesting therapeutic targeting of this signaling axis as a viable option for melanoma treatment.
- 757** **A Runaway PRH/HHEX-Notch3-Positive Feedback Loop Drives Cholangiocarcinoma and Determines Response to CDK4/6 Inhibition**
Philip Kitchen, Ka Ying Lee, Danielle Clark, Nikki Lau, Jomnarong Lertsuwan, Anyaporn Sawasdichai, Jutamaad Satayavivad, Sebastian Oltean, Simon Afford, Kevin Gaston, and Padma-Sheela Jayaraman
The PRH/HHEX transcription factor is an oncogenic driver in cholangiocarcinoma that confers sensitivity to CDK4/6 inhibitors.
- 771** **Integrin β 4-Targeted Cancer Immunotherapies Inhibit Tumor Growth and Decrease Metastasis**
AC Shasha Ruan, Ming Lin, Yong Zhu, Lawrence Lum, Archana Thakur, Runming Jin, Wenlong Shao, Yalei Zhang, Yangyang Hu, Shiang Huang, Elaine M. Hurt, Alfred E. Chang, Max S. Wicha, and Qiao Li
Immune targeting of ITGB4 may represent a novel approach to improve the efficacy of current cancer immunotherapies.

- 784** **IL6/STAT3 Signaling Orchestrates Premetastatic Niche Formation and Immunosuppressive Traits in Lung**
Bo Jing, Tong Wang, Beibei Sun, Jianhua Xu, Dongliang Xu, Yueling Liao, Hongyong Song, Wenzheng Guo, Kaimi Li, Min Hu, Siwei Zhang, Jing Ling, Yanbin Kuang, Tuo Zhang, Binhua P. Zhou, Feng Yao, and Jiong Deng
IL6 plays important roles not only in cell autonomous propensity for metastasis, but also in establishing the metastatic niche.

- 798** **Inhibition of Haspin Kinase Promotes Cell-Intrinsic and Extrinsic Antitumor Activity**
Johannes C. Melms, Sreeram Vallabhaneni, Caitlin E. Mills, Clarence Yapp, Jia-Yun Chen, Eugenio Morelli, Patricia Waszyk, Sushil Kumar, Derrick Deming, Nienke Moret, Steven Rodriguez, Kartik Subramanian, Meri Rogava, Adam N.R. Cartwright, Adrienne Luoma, Shaolin Mei, Titus J. Brinker, David M. Miller, Alexander Spektor, Dirk Schadendorf, Nicolo Riggi, Kai W. Wucherpennig, Peter K. Sorger, and Benjamin Izar
HASPIN inhibition by CX-6258 is a novel and potent strategy for RAF/MEK inhibitor-resistant melanoma and potentially other tumor types. HASPIN inhibition has direct antitumor activity and induces a favorable immune microenvironment.

- 811** **Sustained Coevolution in a Stochastic Model of Cancer-Immune Interaction**
Jason T. George and Herbert Levine
The early cancer-immune interaction sculpts intratumor heterogeneity through the selection of immune-evasive clones. This study provides a mathematical framework for investigating the coevolution between an immune-evasive cancer population and the adaptive immune system.

TRANSLATIONAL SCIENCE

- 820** **A Tumor-in-Host DEB-Based Approach for Modeling Cachexia and Bevacizumab Resistance**
Elena M. Tosca, Maurizio Rocchetti, Enrico Pesenti, and Paolo Magni
A mathematical model describes tumor growth in animal models, taking into consideration the energy balance involving both the growth of tumor and the physiologic functions of the host.
- 832** **Aurora A Kinase Inhibition Destabilizes PAX3-FOXO1 and MYCN and Synergizes with Navitoclax to Induce Rhabdomyosarcoma Cell Death**
AC Johannes Ommer, Joanna L. Selfe, Marco Wachtel, Eleanor M. O'Brien, Dominik Laubscher, Michaela Roemmele, Stephanie Kasper, Olivier Delattre, Didier Surdez, Gemma Petts, Anna Kelsey, Janet Shipley, and Beat W. Schäfer
These findings show that Aurora kinase A and Bcl-2 family proteins are potential targets for FP-RMS.

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843 Combined MEK and PI3K/p110 β Inhibition as a Novel Targeted Therapy for Malignant Mesothelioma Displaying Sarcomatoid Features

Miriam Marqués, Robin Tranchant, Blanca Risa-Ebrí, María L. Suárez-Solís, Luis C. Fernández, Enrique Carrillo-de-Santa-Pau, Natalia del Pozo, Jaime Martínez de Villarreal, Clément Meiller, Yves Allory, Yuna Blum, Christine Pirker, Balazs Hegedus, Simon T. Barry, Amancio Carnero, Walter Berger, Didier Jean, and Francisco X. Real

Mesothelioma is highly aggressive; its sarcomatoid variants have worse prognosis. Building on a genetic mouse model, a novel combination therapy is uncovered that is relevant to human tumors.

857 Rare *BRIP1* Missense Alleles Confer Risk for Ovarian and Breast Cancer

Cassandra L. Moyer, Jennifer Ivanovich, Jessica L. Gillespie, Rachel Doberstein, Marc R. Radke, Marcy E. Richardson, Scott H. Kaufmann, Elizabeth M. Swisher, and Paul J. Goodfellow

Functional characterization of rare variants of uncertain significance in *BRIP1* revealed that 75% demonstrate loss-of-function activity, suggesting rare missense alleles in *BRIP1* confer risk for both breast and ovarian cancer.

868 Mathematical Modeling of Preclinical Alpha-Emitter Radiopharmaceutical Therapy

Alireza Karimian, Nathan T. Ji, Hong Song, and George Sgouros

Modeling is used to optimize α RPT.

877 Murine Oviductal High-Grade Serous Carcinomas Mirror the Genomic Alterations, Gene Expression Profiles, and Immune Microenvironment of Their Human Counterparts

Kevin W. McCool, Zachary T. Freeman, Yali Zhai, Rong Wu, Kevin Hu, Chia-Jen Liu, Scott A. Tomlins, Eric R. Fearon, Brian Magnuson, Rork Kuick, and Kathleen R. Cho

The acquired gene mutations, broad genomic alterations, and gene expression and immune cell-tumor axis changes in a mouse model of oviductal serous carcinoma closely mirror those of human tubo-ovarian high-grade serous carcinoma.

890 NAMPT Inhibition Suppresses Cancer Stem-like Cells Associated with Therapy-Induced Senescence in Ovarian Cancer

Timothy Nacarelli, Takeshi Fukumoto, Joseph A. Zundell, Nail Fatkhutdinov, Stephanie Jean, Mark G. Cadungog, Mark E. Borowsky, and Rugang Zhang

This study highlights the importance of NAMPT-mediated NAD⁺ biosynthesis in the production of cisplatin-induced senescence-associated cancer stem cells, as well as tumor relapse after cisplatin treatment.

CONVERGENCE AND TECHNOLOGIES

901 Cell Adhesiveness Serves as a Biophysical Marker for Metastatic Potential

Pranjali Beri, Anna Popravko, Benjamin Yeoman, Aditya Kumar, Kevin Chen, Enio Hodzic, Alyssa Chiang, Afsheen Banisadr, Jesse K. Placone, Hannah Carter, Stephanie I. Fraley, Parag Katira, and Adam J. Engler

Cancer cells exhibit heterogeneity in adhesivity, which can be used to predict metastatic potential.

RESOURCE REPORT

912 A Versatile ES Cell-Based Melanoma Mouse Modeling Platform

Ilah Bok, Olga Vera, Xiaonan Xu, Neel Jasani, Koji Nakamura, Jordan Reff, Arianna Nenci, Jose G. Gonzalez, and Florian A. Karreth

This study presents a high-throughput and versatile ES cell-based mouse modeling platform that can be combined with state-of-the-art genetic tools to address unanswered questions in melanoma *in vivo*.

See related commentary, p. 655

CORRECTIONS

922 Correction: Hypoxic Tumor-Derived Exosomal miR-301a Mediates M2 Macrophage Polarization via PTEN/PI3K γ to Promote Pancreatic Cancer Metastasis

Xiaofeng Wang, Guangtao Luo, Kundong Zhang, Jun Cao, Chen Huang, Tao Jiang, Bingya Liu, Liping Su, and Zhengjun Qiu

923 Correction: HDAC3 Deficiency Promotes Liver Cancer through a Defect in H3K9ac/H3K9me3 Transition

Hongjie Ji, Yongjie Zhou, Xiang Zhuang, Yongjie Zhu, Zhenru Wu, Yannrong Lu, Shengfu Li, Yong Zeng, Qing R Lu, Yanying Huo, Yujun Shi, and Hong Bu

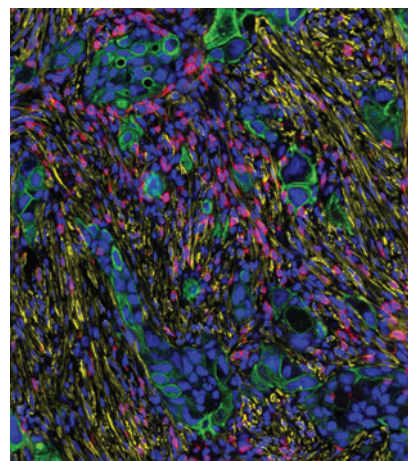
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ABOUT THE COVER

Shining a light on cholangiocarcinoma. NanoString imaging highlights spatial interactions between tumor cells (green), T cells (red), and stromal cells (yellow) within the cholangiocarcinoma tumor microenvironment. The recruitment of immune cells, activation of stromal cells, and proliferation of epithelial cells is a feature of cholangiocarcinoma. Dysregulation of WNT and NOTCH signaling pathways is critical to proliferation and invasion and occurs through activation of the PRH transcription factor, which is thereby able to increase epithelial-mesenchymal plasticity and transit through the cell cycle. Image collected by Dr. Jingjing Gong (NanoString), Dr. Isioma Egbuniwe (histopathologist, University of Nottingham, United Kingdom), Professor K. Gaston (University of Nottingham), and Dr. P.S. Jayaraman (University of Birmingham, United Kingdom). For details, see article by Kitchen and colleagues on page 757.



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