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Tzeh K. Foo, Gabriele Vincelli, Eric Huselid, Joonyoung Her, Haiyan Zheng, Srilatha Simhadri, Meiling Wang, Yanying Huo, Tao Li, Xiaochun Yu, Hong Li, Weixing Zhao, Samuel F. Bunting, and Bing Xia
This study identifies a BRCA1 phosphorylation event critical for its DNA repair function and reveals the functional defects of several BRCA1 variants of unknown significance.

RESOURCE REPORT

- 4685** **Lentiviral-Driven Discovery of Cancer Drug Resistance Mutations**
Paul Yenerall, Rahul K. Kollipara, Kimberley Avila, Michael Peyton, Christopher A. Eide, Daniel Bottomly, Shannon K. McWeeney, Yan Liu, Kenneth D. Westover, Brian J. Druker, John D. Minna, and Ralf Kittler
LentiMutate can evaluate a drug's on-target activity and can nominate resistance mutations before they occur in patients, which could accelerate and refine drug development to increase the survival of patients with cancer.

GENOME AND EPIGENOME

- 4696** **PAX9 Determines Epigenetic State Transition and Cell Fate in Cancer**
Zibo Zhao, Aileen P. Szczepanski, Natsumi Tsuboyama, Hiam Abdala-Valencia, Young Ah Goo, Benjamin D. Singer, Elizabeth T. Bartom, Feng Yue, and Lu Wang
A genome-wide screen in small cell lung cancer reveals PAX9/NuRD-mediated epigenetic enhancer silencing and tumor progression, supporting the development of novel personalized therapeutic approaches targeting the PAX9-regulated network.

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4709 **Acquired *RAD51C* Promoter Methylation Loss Causes PARP Inhibitor Resistance in High-Grade Serous Ovarian Carcinoma**

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Homozygous *RAD51C* methylation is a positive predictive biomarker for sensitivity to PARP inhibitors, whereas a single unmethylated gene copy is sufficient to confer resistance.

MOLECULAR CELL BIOLOGY

4723 **Autocrine GM-CSF Signaling Contributes to Growth of HER2⁺ Breast Leptomeningeal Carcinomatosis**

Khairul I. Ansari, Arunoday Bhan, Mika Saotome, Antariksh Tyagi, Bony De Kumar, Clara Chen, Motoki Takaku, and Rahul Jandial

This study characterizes molecular mechanisms that drive HER2⁺ leptomeningeal carcinomatosis and demonstrates the efficacy of anti-GM-CSF antibodies and pan-Aurora kinase inhibitors against this disease.

4736 **RNA Splicing Factors *SRRM3* and *SRRM4* Distinguish Molecular Phenotypes of Castration-Resistant Neuroendocrine Prostate Cancer**

Mark P. Labrecque, Lisha G. Brown, Ilsa M. Coleman, Bryce Lakely, Nicholas J. Brady, John K. Lee, Holly M. Nguyen, Dapei Li, Brian Hanratty, Michael C. Haffner, David S. Rickman, Lawrence D. True, Daniel W. Lin, Hung-Ming Lam, Joshi J. Alumkal, Eva Corey, Peter S. Nelson, and Colm Morrissey

This study identifies *SRRM3* as a key inducer of cellular plasticity in prostate cancer with neuroendocrine features and delineates distinct neuroendocrine phenotypes to inform therapeutic development and precision medicine applications.

4751 **TGF β Signaling Activated by Cancer-Associated Fibroblasts Determines the Histological Signature of Lung Adenocarcinoma**

Ryo Sato, Kosuke Imamura, Takashi Semba, Yusuke Tomita, Sho Saeki, Koei Ikeda, Yoshihiro Komohara, Makoto Suzuki, Takuro Sakagami, Hideyuki Saya, and Yoshimi Arima

CAFs secrete TGF β to induce a solid-to-acinar transition in lung cancer cells, demonstrating how the tumor microenvironment influences histological patterns and tumor heterogeneity in lung adenocarcinoma.

TUMOR BIOLOGY AND IMMUNOLOGY

4766 **Multiple Roles of IL6 in Hepatic Injury, Steatosis, and Senescence Aggregate to Suppress Tumorigenesis**

Anat Shriki, Tali Lanton, Amir Sonnenblick, Orr Levkovitch-Siany, Dana Eidelstein, Rinat Abramovitch, Nofar Rosenberg, Orit Pappo, Sharona Elgavish, Yuval Nevo, Rifaat Safadi, Amnon Peled, Stefan Rose-John, Eithan Galun, and Jonathan H. Axelrod

These findings describe a context-dependent role of IL6 signaling in hepatocarcinogenesis and predict that increased IL6-neutralizing sgp130 levels in some patients with NASH may herald early HCC development.

See related commentary, p. 4671

4778 **M⁶A Demethylase ALKBH5 Regulates PD-L1 Expression and Tumor Immunoenvironment in Intrahepatic Cholangiocarcinoma**

Xinyao Qiu, Shuai Yang, Shan Wang, Jianmin Wu, Bo Zheng, Kaiting Wang, Siyun Shen, Seongsong Jeong, Zhixuan Li, Yanjing Zhu, Tong Wu, Xuan Wu, Rui Wu, Weiwei Liu, Hong-Yang Wang, and Lei Chen

This study identifies PD-L1 mRNA as a target of ALKBH5 and reveals a role for ALKBH5 in regulating the tumor immune microenvironment and immunotherapy efficacy.

4794 **Targeting the Extracellular HSP90 Co-Chaperone Morgana Inhibits Cancer Cell Migration and Promotes Anticancer Immunity**

Laura Secli, Lidia Avalor, Pietro Poggio, Giuseppe Fragale, Cristiana Cannata, Laura Conti, Andrea Iannucci, Giovanna Carrà, Cristina Rubinetto, Barbara Miniscalco, Emilio Hirsch, Valeria Poli, Alessandro Morotti, Marco De Andrea, Emilia Turco, Federica Cavallo, Federica Fusella, and Mara Brancaccio

This work suggests the potential therapeutic value of targeting the extracellular HSP90 co-chaperone Morgana to inhibit metastasis formation and enhance the CD8⁺ T-cell-mediated antitumor immune response.

TRANSLATIONAL SCIENCE

4808 **FLASH Proton Radiotherapy Spares Normal Epithelial and Mesenchymal Tissues While Preserving Sarcoma Response**

Anastasia Velopoulou, Ilias V. Karagounis, Gwendolyn M. Cramer, Michele M. Kim, Giorgos Skoufos, Denisa Goia, Sarah Hagan, Ioannis I. Verginadis, Khayrullo Shoniyozov, June Chiango, Michelle Cerullo, Kelley Varner, Lutian Yao, Ling Qin, Artemis G. Hatzigeorgiou, Andy J. Minn, Mary Putt, Matthew Lanza, Charles-Antoine Assenmacher, Enrico Radaelli, Jennifer Huck, Eric Diffenderfer, Lei Dong, James Metz, Constantinos Koumenis, Keith A. Cengel, Amit Maity, and Theresa M. Busch

These findings will spur investigation of FLASH radiotherapy in sarcoma and additional cancers where mesenchymal tissues are at risk, including head and neck cancer, breast cancer, and pelvic malignancies.

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4822 Targeting c-Myc to Overcome Acquired Resistance of EGFR Mutant NSCLC Cells to the Third-Generation EGFR Tyrosine Kinase Inhibitor, Osimertinib

Lei Zhu, Zhen Chen, Hongjing Zang, Songqing Fan, Jiajia Gu, Guojing Zhang, Kevin D.-Y. Sun, Qiming Wang, Yong He, Taofeek K. Owonikoko, Suresh S. Ramalingam, and Shi-Yong Sun

This study demonstrates a critical role of c-Myc modulation in mediating therapeutic efficacy of osimertinib including osimertinib acquired resistance and suggests targeting c-Myc as a potential strategy to overcome osimertinib acquired resistance.

4835 Single-Cell Analyses Reveal Diverse Mechanisms of Resistance to EGFR Tyrosine Kinase Inhibitors in Lung Cancer

Yukie Kashima, Daisuke Shibahara, Ayako Suzuki, Kyoko Muto, Ikei S. Kobayashi, David Plotnick, Hibiki Udagawa, Hiroki Izumi, Yuji Shibata, Kosuke Tanaka, Masanori Fujii, Akihiro Ohashi, Masahide Seki, Koichi Goto, Katsuya Tsuchihara, Yutaka Suzuki, and Susumu S. Kobayashi

Single-cell analyses identify diverse mechanisms of resistance as well as the state of tolerant cells that give rise to resistance to EGFR tyrosine kinase inhibitors.

4849 Multiparametric Photoacoustic Analysis of Human Thyroid Cancers *In Vivo*

Jeesu Kim, Byullee Park, Jeonghoon Ha, Idan Steinberg, Sarah M. Hooper, Chaiho Jeong, Eun-Yeong Park, Wonseok Choi, Tie Liang, Ja Seong Bae, Ravi Managuli, Yongmin Kim, Sanjiv S. Gambhir, Dong-Jun Lim, and Chulhong Kim

This report highlights a novel photoacoustic scoring method for risk stratification of thyroid nodules, where malignancy of the nodules can be diagnosed with 83% sensitivity and 93% specificity.

CONVERGENCE AND TECHNOLOGIES

4861 Mathematical Modeling and Mutational Analysis Reveal Optimal Therapy to Prevent Malignant Transformation in Grade II IDH-Mutant Gliomas

Kosuke Aoki, Hiromichi Suzuki, Takashi Yamamoto, Kimiyo N. Yamamoto, Sachi Maeda, Yusuke Okuno, Melissa Ranjit, Kazuya Motomura, Fumiharu Ohka, Kuniaki Tanahashi, Masaki Hirano, Tomohide Nishikawa, Hiroyuki Shimizu, Yotaro Kitano, Junya Yamaguchi, Shintaro Yamazaki, Hideo Nakamura, Masamichi Takahashi, Yoshitaka Narita, Mitsutoshi Nakada, Shoichi Deguchi, Masahiro Mizoguchi, Yasutomo Momii, Yoshihiro Muragaki, Tatsuya Abe, Jiro Akimoto, Toshihiko Wakabayashi, Ryuta Saito, Seishi Ogawa, Hiroshi Haeno, and Atsushi Natsume

A mathematical model successfully estimates malignant transformation-free survival and reveals a link between genetic alterations and progression, identifying precision medicine approaches for optimal treatment of IDH-mutant low-grade gliomas.

4874 Mapping Mechanical Properties of the Tumor Microenvironment by Laser Speckle Rheological Microscopy

Zeinab Hajjarian, Elena F. Brachtel, Diane M. Tshikudi, and Seemantini K. Nadkarni

Laser speckle rheological microscopy establishes the links between microscale heterogeneities of viscoelasticity and histopathological subtype, tumor grade, receptor expression, as well as lymph node status in breast carcinoma.

ABOUT THE COVER

Mechanical makeover of the tissue microenvironment has emerged as both the cause and the consequence of the breast carcinogenesis. Laser Speckle Rheological microscopy (SHEAR) maps the viscoelastic properties of the tissue microenvironment with high spatial resolution (~50 μm). The cover displays the SHEAR map of viscoelastic moduli for an invasive ductal carcinoma of the breast featuring the stiff tumor stroma (red to magenta to purple hues) in striking contrast with the soft tumor epithelium (blue to green to yellow hues). In human breast tumors, micromechanical metrics including heterogeneity and gradients of viscoelastic moduli measured by SHEAR are associated with histological subtype, grade, molecular expressions, and nodal status. For details, see the article by Hajjarian and colleagues on page 4874.

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