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Tzeh Keong Foo and Bing Xia

## CANCER RESEARCH HIGHLIGHTS

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Inna Smalley and Keiran S.M. Smalley  
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## GENOME AND EPIGENOME

- 3201**     **Genetic Risk of Second Primary Cancer in Breast Cancer Survivors: The Multiethnic Cohort Study**  
Fei Chen, Sungshim L. Park, Lynne R. Wilkens, Peggy Wan, Steven N. Hart, Chunling Hu, Siddhartha Yadav, Fergus J. Couch, David V. Conti, Adam J. de Smith, and Christopher A. Haiman  
This multiethnic study links germline pathogenic variants in *BRCA1*, *BRCA2*, and *ERCC2* to the development of second primary cancer in breast cancer survivors, providing biological insights and biomarkers to guide patient monitoring.

## METABOLISM AND CHEMICAL BIOLOGY

- 3209**     **GLS2 Is a Tumor Suppressor and a Regulator of Ferroptosis in Hepatocellular Carcinoma**  
Sawako Suzuki, Divya Venkatesh, Hiroaki Kanda, Akitoshi Nakayama, Hiroyuki Hosokawa, Eunyoung Lee, Takashi Miki, Brent R. Stockwell, Koutaro Yokote, Tomoaki Tanaka, and Carol Prives  
This study demonstrates that the key regulator of glutaminolysis, GLS2, can limit HCC *in vivo* by promoting ferroptosis through  $\alpha$ KG-dependent lipid ROS, which in turn might lay the foundation for a novel therapeutic approach.

- 3223**     **GOT2 Silencing Promotes Reprogramming of Glutamine Metabolism and Sensitizes Hepatocellular Carcinoma to Glutaminase Inhibitors**

Yunzheng Li, Binghua Li, Yanchao Xu, Liyuan Qian, Tiancheng Xu, Gang Meng, Huan Li, Ye Wang, Laizhu Zhang, Xiang Jiang, Qi Liu, Yuanyuan Xie, Chunxiao Cheng, Beicheng Sun, and Decai Yu  
Altered glutamine metabolism induced by *GOT2* loss supports HCC growth and metastasis but confers a targetable vulnerability to glutaminase inhibitors.

## MOLECULAR CELL BIOLOGY

- 3236**     **Single-Cell Transcriptome Profiling Reveals Intratumoral Heterogeneity and Molecular Features of Ductal Carcinoma *In Situ***  
Momoko Tokura, Jun Nakayama, Marta Prieto-Vila, Sho Shiino, Masayuki Yoshida, Tomofumi Yamamoto, Naoaki Watanabe, Shin Takayama, Yutaka Suzuki, Koji Okamoto, Takahiro Ochiya, Takashi Kohno, Yasushi Yatabe, Akihiko Suto, and Yusuke Yamamoto  
Investigation of the molecular features of ductal carcinoma *in situ* at single cell resolution provides new insights into breast cancer biology and identifies candidate therapeutic targets and diagnostic biomarkers.

- 3249**     **And-1 Coordinates with the FANCM Complex to Regulate Fanconi Anemia Signaling and Cisplatin Resistance**  
Yi Zhang, Jing Li, Yuan Zhou, Zhuqing Li, Changmin Peng, Huadong Pei, and Wenge Zhu  
This work shows that phosphorylation of And-1 by ATR activates Fanconi anemia signaling at interstrand crosslink-stalled replication forks by recruiting the FANCM/FAAP24 complex, revealing And-1 as a potential therapeutic target in cancer.

- 3263**     **Activating mTOR Mutations Are Detrimental in Nutrient-Poor Conditions**  
Agata A. Bielska, Caitlin F. Harrigan, Yeon Ju Kyung, Quaid Morris, Wilhelm Palm, and Craig B. Thompson  
This study suggests that cells need to inactivate mTOR to survive nutrient stress, which could explain the rarity of mTOR mutations and the limited clinical activity of mTOR inhibitors in cancer.

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## TUMOR BIOLOGY AND IMMUNOLOGY

**3275 Mapping the Immune Landscape in Metastatic Melanoma Reveals Localized Cell–Cell Interactions That Predict Immunotherapy Response**

Asier Antoranz, Yannick Van Herck, Maddalena M. Bolognesi, Seodhna M. Lynch, Arman Rahman, William M. Gallagher, Veerle Boecxstaens, Jean-Christophe Marine, Giorgio Cattoretto, Joost J. van den Oord, Frederik De Smet, Oliver Bechter, and Francesca M. Bosisio

This study shows that spatial characterization can address the challenge of finding efficient biomarkers, revealing that localization of macrophages and T cells in melanoma predicts patient response to ICI.

See related commentary, p. 3198

**3291 Lipid-Associated Macrophages Are Induced by Cancer-Associated Fibroblasts and Mediate Immune Suppression in Breast Cancer**

Eleonora Timperi, Paul Gueguen, Martina Molgora, Ilaria Magagna, Yann Kieffer, Silvia Lopez-Lastra, Philemon Sirven, Laura G. Baudrin, Sylvain Baulande, André Nicolas, Gabriel Champenois, Didier Meseure, Anne Vincent-Salomon, Anne Tardivon, Enora Laas, Vassili Soumelis, Marco Colonna, Fatima Mechta-Grigoriou, Sebastian Amigorena, and Emanuela Romano

This work identifies a novel lipid-associated macrophage subpopulation with immune suppressive functions, offering new leads for therapeutic interventions in triple-negative breast cancer.

**3307 PIM2 Expression Induced by Proinflammatory Macrophages Suppresses Immunotherapy Efficacy in Hepatocellular Carcinoma**

Jun-Cheng Wang, Dong-Ping Chen, Shi-Xun Lu, Jin-Bin Chen, Yuan Wei, Xue-Chao Liu, Yu-Hao Tang, Rongxin Zhang, Jian-Cong Chen, Anna Kan, Li Xu, Yao-Jun Zhang, Jiajie Hou, Dong-Ming Kuang, Min-Shan Chen, and Zhong-Guo Zhou

Cross-talk between T cells and macrophages regulates cancer cell PIM2 expression to promote cancer aggressiveness, revealing translational approaches to improve response to ICB in hepatocellular carcinoma.

**3321  $\beta$ 2-Microglobulin Maintains Glioblastoma Stem Cells and Induces M2-like Polarization of Tumor-Associated Macrophages**

Daqi Li, Qian Zhang, Lu Li, Kexin Chen, Junlei Yang, Deobrat Dixit, Ryan C. Gimple, Shusheng Ci, Chenfei Lu, Lang Hu, Jiancheng Gao, Danyang Shan, Yangqing Li, Junxia Zhang, Zhumei Shi, Danling Gu, Wei Yuan, Qiulian Wu, Kailin Yang, Linjie Zhao, Zhixin Qiu, Deguang Lv, Wei Gao, Hui Yang, Fan Lin, Qianghu Wang, Jianghong Man, Chaojun Li, Weiwei Tao, Sameer Agnihotri, Xu Qian, Yu Shi, Yongping You, Nu Zhang, Jeremy N. Rich, and Xiuxing Wang

$\beta$ 2-microglobulin signaling in glioblastoma cells activates a PI3K/AKT/MYC/TGF $\beta$ 1 axis that maintains stem cells and induces M2-like macrophage polarization, highlighting potential therapeutic strategies for targeting tumor cells and the immunosuppressive microenvironment in glioblastoma.

## TRANSLATIONAL SCIENCE

**3335 Targeting RAS Mutant Colorectal Cancer with Dual Inhibition of MEK and CDK4/6**

Alexey V. Sorokin, Preeti Kanikarla Marie, Lea Bitner, Muddassir Syed, Melanie Woods, Ganiraju Manyam, Lawrence N. Kwong, Benny Johnson, Van K. Morris, Philip Jones, David G. Menter, Michael S. Lee, and Scott Kopetz

This co-clinical trial of combined MEK-CDK4/6 inhibition in RAS mutant colorectal cancer demonstrates therapeutic efficacy in patient-derived xenografts and safety in patients, identifies biomarkers of response, and uncovers targetable mechanisms of resistance.

**3345 Alternative Lengthening of Telomeres in Cancer Confers a Vulnerability to Reactivation of p53 Function**

Shawn J. Macha, Balakrishna Koneru, Trevor A. Burrow, Charles Zhu, Dzmitry Savitski, Rakhshanda L. Rahman, Catherine A. Ronaghan, Jonas Nance, Kristyn McCoy, Cody Eslinger, and C. Patrick Reynolds

This work demonstrates that constitutive activation of ATM in chemotherapy-refractory ALT cancer cells renders them hypersensitive to reactivation of p53 function by APR-246, indicating a potential strategy to overcome therapeutic resistance.

**3359 CDK4/6 Inhibition Enhances Oncolytic Virus Efficacy by Potentiating Tumor-Selective Cell Killing and T-cell Activation in Refractory Glioblastoma**

Jingshu Xiao, Jiaming Liang, Junjie Fan, Panpan Hou, Xiaodong Li, Haipeng Zhang, Kai Li, Lang Bu, Ping Li, Miao He, Yongheng Zhong, Liping Guo, Penghui Jia, Qiaoqiao Xiao, Junyu Wu, Hong Peng, Chunmei Li, Fan Xing, and Deyin Guo

This study proposes inhibition of cyclin-dependent kinases as a clinically translatable combinatorial strategy to enhance the efficacy of oncolytic virotherapy in GBM.

**3375 Pharmacologic Targeting of TFIID Suppresses KRAS-Mutant Pancreatic Ductal Adenocarcinoma and Synergizes with TRAIL**

Russell Moser, James Annis, Olga Nikolova, Cliff Whatcott, Kay Gurley, Eduardo Mendez, Kim Moran-Jones, Craig Dorrell, Rosalie C. Sears, Calvin Kuo, Haiyong Han, Andrew Biankin, Carla Grandori, Daniel D. Von Hoff, and Christopher J. Kemp

This study utilizes functional genetic and pharmacological profiling of KRAS-mutant pancreatic adenocarcinoma to identify therapeutic strategies and finds that TFIID inhibition synergizes with TRAIL to induce apoptosis in KRAS-driven pancreatic cancer.

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## CONVERGENCE AND TECHNOLOGIES

### 3394 **MRI-Based Digital Models Forecast Patient-Specific Treatment Responses to Neoadjuvant Chemotherapy in Triple-Negative Breast Cancer**

Chengyue Wu, Angela M. Jarrett, Zijian Zhou, Nabil Elshafeey, Beatriz E. Adrada, Rosalind P. Candelaria, Rania M.M. Mohamed, Medine Boge, Lei Huo, Jason B. White, Debu Tripathy, Vicente Valero, Jennifer K. Litton, Clinton Yam, Jong Bum Son, Jingfei Ma, Gaiane M. Rauch, and Thomas E. Yankeelov

Integrating MRI data with biologically based mathematical modeling successfully predicts breast cancer response to chemotherapy, suggesting digital twins could facilitate a paradigm shift from simply assessing response to predicting and optimizing therapeutic efficacy.

## RETRACTIONS

### 3405 **Retraction: Characterization of Phosphoglycerate Kinase-1 Expression of Stromal Cells Derived from Tumor Microenvironment in Prostate Cancer Progression**

Jianhua Wang, Gigi Ying, Jingchen Wang, Younghun Jung, Jian Lu, Jiang Zhu, Kenneth J. Pienta, and Russell S. Taichman

### 3406 **Retraction: CXCR6 Induces Prostate Cancer Progression by the AKT/Mammalian Target of Rapamycin Signaling Pathway**

Jianhua Wang, Yi Lu, Jingchen Wang, Alisa E. Koch, Jian Zhang, and Russell S. Taichman

## ABOUT THE COVER

High-dimensional tissue multiplexing provides spatial information that is crucial in identifying important cell-cell interactions and the dynamics of marker expression. On the basis of the expression of 50+ proteins stained *in situ* and at the single-cell level with a conventional immunofluorescence technique, the cells that are present in the tissue are clustered and given a phenotypic label that is assigned a specific color. Every cell after phenotypic color labeling is placed back in the original tissue context, generating a digital tissue, which is a powerful visualization tool. The cover image shows a multiplex image (left) and the digital tissue (right) of metastatic melanoma in a lymph node. Left side, partial visualization of 5 of the 50+ markers that have been multiplexed: green, CD20; yellow, CD3; red, MelanA; pink, S100B; blue, DAPI. Right side, digital tissue: green, B cells; yellow, T cells; red, melanoma cells; purple, dendritic cells; blue, macrophages; aquamarine, blood vessels; light blue, plasma cells; gray, others. For details, see the article by Antoranz and colleagues on page 3275.

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