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4610 Turning Up the Heat on the Pancreatic Tumor Microenvironment by Epigenetic Priming

Kenneth P. Nephew

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PRIORITY REPORT

4612 ERG-Mediated Coregulator Complex Formation Maintains Androgen Receptor Signaling in Prostate Cancer

Neel Shah, Nikolas Kesten, Alba Font-Tello, Matthew E.K. Chang, Raga Vadhi, Klothilda Lim, Mark R. Flory, Paloma Cejas, Hisham Mohammed, Henry W. Long, and Myles Brown

These findings exploit murine organoid models to uncover the mechanism of ERG-mediated tumorigenesis and subsequent oncogenic dependencies in prostate cancer.

GENOME AND EPIGENOME

4620 EZH2 Regulates Pancreatic Cancer Subtype Identity and Tumor Progression via Transcriptional Repression of *GATA6*

Shilpa Patil, Benjamin Steuber, Waltraut Kopp, Vijayalakshmi Kari, Laura Urbach, Xin Wang, Stefan Küffer, Hanibal Bohnenberger, Dimitra Spyropoulou, Zhe Zhang, Lennart Versemann, Mark Sebastian Bösherz, Marius Brunner, Jochen Gaedcke, Philipp Ströbel, Jin-San Zhang, Albrecht Neesse, Volker Ellenrieder, Shiv K. Singh, Steven A. Johnsen, and Elisabeth Hessmann

This study highlights the role of EZH2 in PDAC progression and molecular subtype identity and suggests EZH2 inhibition as a strategy to recalibrate *GATA6* expression in favor of a less aggressive disease.

4633 KDM5B Is Essential for the Hyperactivation of PI3K/AKT Signaling in Prostate Tumorigenesis

Guoliang Li, Thanigaivelan Kanagasabai, Wenfu Lu, Mike R. Zou, Shang-Min Zhang, Sherly I. Celada, Michael G. Izban, Qi Liu, Tao Lu, Billy R. Ballard, Xinchun Zhou, Samuel E. Adunyah, Robert J. Matusik, Qin Yan, and Zhenbang Chen

This study demonstrates that levels of histone modification enzyme KDM5B determine hyperactivation of PI3K/AKT signaling in prostate cancer and that targeting KDM5B could be a novel strategy against prostate cancer.

4644 A Deep Learning Framework Identifies Pathogenic Noncoding Somatic Mutations from Personal Prostate Cancer Genomes

Cheng Wang and Jingjing Li

This study's characterization of the noncoding genome in prostate cancer reveals mutational signatures predictive of clinical observations, which may serve as a powerful prognostic tool in this disease.

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MOLECULAR CELL BIOLOGY

4655 Hypoxia Induces Resistance to EGFR Inhibitors in Lung Cancer Cells via Upregulation of FGFR1 and the MAPK Pathway

Yuhong Lu, Yanfeng Liu, Sebastian Oeck, Gary J. Zhang, Alexander Schramm, and Peter M. Glazer

Hypoxia-induced resistance to EGFR TKI is driven by overexpression of FGFR1 to sustain ERK signaling, where a subsequent combination of EGFR TKI with FGFR1 inhibitors or MEK inhibitors reverses this resistance.

4668 ERK1/2 Signaling Induces Upregulation of ANGPT2 and CXCR4 to Mediate Liver Metastasis in Colon Cancer

A C

Jelena Urošević, María Teresa Blasco, Alicia Llorente, Anna Bellmunt, Antoni Berenguer-Llergo, Marc Guiu, Adrià Cañellas, Esther Fernandez, Ivan Burkov, Maria Clapés, Mireia Cartanà, Cristina Figueras-Puig, Eduard Batlle, Angel R. Nebreda, and Roger R. Gomis

These findings identify amplified ERK1/2 signaling in *KRAS*-mutated colorectal cancer cells as a driver of tumor–stroma interactions that favor formation of metastases in the liver.

4681 The Alternative Splicing Factor, MBNL1, Inhibits Glioblastoma Tumor Initiation and Progression by Reducing Hypoxia-Induced Stemness

Dillon M. Voss, Anthony Sloan, Raffaella Spina, Heather M. Ames, and Eli E. Bar

This study describes an unexpected mechanism by which RNA-binding protein MBNL1, activity is inhibited in hypoxia by a simple isoform switch to regulate glioma stem cell self-renewal, tumorigenicity, and progression.

4693 FAM46C and FNDC3A Are Multiple Myeloma Tumor Suppressors That Act in Concert to Impair Clearing of Protein Aggregates and Autophagy

Nicola Manfrini, Marilena Mancino, Annarita Miluzio, Stefania Oliveto, Matteo Balestra, Piera Calamita, Roberta Alfieri, Riccardo L. Rossi, Marco Sassoè-Pognetto, Chiara Salio, Alessandro Cuomo, Tiziana Bonaldi, Marcello Manfredi, Emilio Marengo, Elia Ranzato, Simona Martinotti, Davide Cittaro, Giovanni Tonon, and Stefano Biffo

This study identifies a new multiple myeloma-specific tumor suppressor complex that regulates autophagy and unconventional secretion, highlighting the sensitivity of multiple myeloma cells to the accumulation of protein aggregates

TUMOR BIOLOGY AND IMMUNOLOGY

4707 Epigenetic Control of *Cdkn2a.Arf* Protects Tumor-Infiltrating Lymphocytes from Metabolic Exhaustion

A C

Brian Koss, Bradley D. Shields, Erin M. Taylor, Aaron J. Storey, Stephanie D. Byrum, Allen J. Gies, Charity L. Washam, Samrat Roy Choudhury, Jeong Hyun Ahn, Hidetaka Uryu, Jason B. Williams, Kimberly J. Krager, Tung-Chin Chiang, Samuel G. Mackintosh, Rick D. Edmondson, Nukhet Aykin-Burns, Thomas F. Gajewski, Gang Greg Wang, and Alan J. Tackett

These findings demonstrate that manipulation of T-cell EZH2 in cellular therapies may yield cellular products able to withstand solid tumor metabolic-deficient environments.

4720 *Cdkn2a* Loss in a Model of Neurofibroma Demonstrates Stepwise Tumor Progression to Atypical Neurofibroma and MPNST

Katherine E. Chaney, Melissa R. Perrino, Leah J. Kershner, Ami V. Patel, Jianqiang Wu, Kwangmin Choi, Tilat A. Rizvi, Eva Dombi, Sara Szabo, David A. Largaespada, and Nancy Ratner

New mouse models recapitulate the stepwise progression of NF1 tumors and will be useful to define effective treatments that halt tumor growth and tumor progression in NF1.

4731 PET Reporter Gene Imaging and Ganciclovir-Mediated Ablation of Chimeric Antigen Receptor T Cells in Solid Tumors

Surya Murty, Louai Labanieh, Tara Murty, Gayatri Gowrishankar, Tom Haywood, Israt S. Alam, Corinne Beinat, Elise Robinson, Amin Aalipour, Dorota D. Klysz, Jennifer R. Cochran, Robbie G. Majzner, Crystal L. Mackall, and Sanjiv S. Gambhir

This study showcases the only genetically engineered system capable of serving the dual role both as an effective PET imaging reporter and as a suicide switch for CAR T cells.

4741 YAP-Mediated Repression of HRK Regulates Tumor Growth, Therapy Response, and Survival Under Tumor Environmental Stress in Neuroblastoma

Jenny Shim, Jasmine Y. Lee, Hunter C. Jonus, Amanda Arnold, Robert W. Schnepf, Kaitlyn M. Janssen, Victor Maximov, and Kelly C. Goldsmith

This study identifies HRK as a novel tumor suppressor in neuroblastoma and suggests dual MEK and YAP inhibition as a potential therapeutic strategy in *RAS*-hyperactivated neuroblastomas.

4754 A DNA Hypomethylating Drug Alters the Tumor Microenvironment and Improves the Effectiveness of Immune Checkpoint Inhibitors in a Mouse Model of Pancreatic Cancer

Tamas A. Gonda, Jarwei Fang, Martha Salas, Catherine Do, Emily Hsu, Anna Zhukovskaya, Ariel Siegel, Ryota Takahashi, Zoila A. Lopez-Bujanda, Charles G. Drake, Gulam A. Manji, Timothy C. Wang, Kenneth P. Olive, and Benjamin Tycko

In a pancreatic cancer model, a DNA hypomethylating drug increases tumor-infiltrating effector T cells, increases a subset of M2 macrophages, and significantly prolongs survival in combination with immune checkpoint inhibitors.

See related commentary, p. 4610

4768 YAP and AP-1 Cooperate to Initiate Pancreatic Cancer Development from Ductal Cells in Mice

Jaeh Park, David Eisenbarth, Wonyoung Choi, Hail Kim, Chan Choi, Dahye Lee, and Dae-Sik Lim

A pancreatic ductal cell-specific knockout mouse model featuring constitutively active YAP allows for the study of YAP-dependent transformation of the pancreas and for screening pharmacologically active inhibitors.

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- 4780** **Visualization of Activated T Cells by OX40-ImmunoPET as a Strategy for Diagnosis of Acute Graft-versus-Host Disease**
AC Israt S. Alam, Federico Simonetta, Lukas Scheller, Aaron T. Mayer, Surya Murty, Ophir Vermesh, Tomomi W. Nobashi, Juliane K. Lohmeyer, Toshihito Hirai, Jeanette Baker, Kenneth H. Lau, Robert Negrin, and Sanjiv S. Gambhir
OX40-immunoPET imaging is a promising noninvasive strategy for early detection of GvHD, capable of detecting signs of GvHD pathology even prior to the development of overt clinical symptoms.
- 4791** **Oncogenic TRIM37 Links Chemoresistance and Metastatic Fate in Triple-Negative Breast Cancer**
Piotr Przanowski, Song Lou, Rachisan Djiak Tihagam, Tanmoy Mondal, Caroline Conlan, Gururaj Shivange, Ilyas Saltani, Chandrajeet Singh, Kun Xing, Benjamin B. Morris, Marty W. Mayo, Luis Teixeira, Jacqueline Lehmann-Che, Jogender Tushir-Singh, and Sanchita Bhatnagar
TRIM37 drives aggressive TNBC biology by promoting resistance to chemotherapy and inducing a prometastatic transcriptional program; inhibition of TRIM37 increases chemotherapy efficacy and reduces metastasis risk in patients with TNBC.
- 4805** **CRISPR/Cas9-Mediated Point Mutation in *Nkx3.1* Prolongs Protein Half-Life and Reverses Effects *Nkx3.1* Allelic Loss**
Cai Bowen, Maho Shibata, Hailan Zhang, Sarah K. Bergren, Michael M. Shen, and Edward P. Gelmann
These findings show that prolonging the half-life of *Nkx3.1* reduces proliferation, enhances DNA end-labeling, and protects from DNA damage, ultimately blocking the preneoplastic effects of *Nkx3.1* allelic loss.
- 4828** **Breast Cancer Cell Detection and Characterization from Breast Milk-Derived Cells**
Poornima Bhat-Nakshatri, Brijesh Kumar, Ed Simpson, Kandice K. Ludwig, Mary L. Cox, Hongyu Gao, Yunlong Liu, and Hari Krishna Nakshatri
These findings describe how a simple method for characterization of cancer cells in pregnancy and postpartum breast cancer can be exploited as a surveillance tool for women at risk of developing breast cancer.
- 4840** **Allosteric SHP2 Inhibitor, IACS-13909, Overcomes EGFR-Dependent and EGFR-Independent Resistance Mechanisms toward Osimertinib**
AC Yuting Sun, Brooke A. Meyers, Barbara Czako, Paul Leonard, Faika Msee, Angela L. Harris, Qi Wu, Sarah Johnson, Connor A. Parker, Jason B. Cross, Maria Emilia Di Francesco, Benjamin J. Bivona, Christopher A. Bristow, Jason P. Burke, Caroline C. Carrillo, Christopher L. Carroll, Qing Chang, Ningping Feng, Guang Gao, Sonal Gera, Virginia Giuliani, Justin K. Huang, Yongying Jiang, Zhijun Kang, Jeffrey J. Kovacs, Chiu-Yi Liu, Anastasia M. Lopez, Xiaoyan Ma, Pijus K. Mandal, Timothy McAfoos, Meredith A. Miller, Robert A. Mullinax, Michael Peoples, Vandhana Ramamoorthy, Sahil Seth, Nakiya D. Spencer, Erika Suzuki, Christopher C. Williams, Simon S. Yu, Andy M. Zuniga, Giulio F. Draetta, Joseph R. Marszalek, Timothy P. Heffernan, Nancy E. Kohl, and Philip Jones
These findings highlight the discovery of IACS-13909 as a potent, selective inhibitor of SHP2 with drug-like properties, and targeting SHP2 may serve as a therapeutic strategy to overcome tumor resistance to osimertinib.

CONVERGENCE AND TECHNOLOGIES

- 4854** **Integrated Genomic Characterization of the Human Immunome in Cancer**
Yongsheng Li, Brandon Burgman, Daniel J. McGrail, Ming Sun, Dan Qi, Sachet A. Shukla, Erxi Wu, Anna Capasso, Shiao-Yih Lin, Catherine J. Wu, S. Gail Eckhardt, Gordon B. Mills, Bo Li, Nidhi Sahni, and S. Stephen Yi
This study demonstrates that integration of multiomics data can help identify critical molecular determinants for effective targeted therapeutics.

TRANSLATIONAL SCIENCE

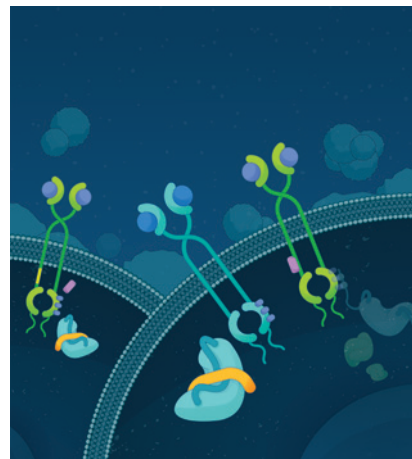
- 4815** **5-Fluorouracil Enhances the Antitumor Activity of the Glutaminase Inhibitor CB-839 against PIK3CA-Mutant Colorectal Cancers**
Yiqing Zhao, Xiujing Feng, Yicheng Chen, J. Eva Selfridge, Shashank Gorityala, Zhanwen Du, Janet M. Wang, Yujun Hao, Gino Cioffi, Ronald A. Conlon, Jill S. Barnholtz-Sloan, Joel Saltzman, Smitha S. Krishnamurthi, Shaveta Vinayak, Martina Veigl, Yan Xu, David L. Bajor, Sanford D. Markowitz, Neal J. Meropol, Jennifer R. Eads, and Zhenghe Wang
Preclinical and clinical trial data suggest that the combination of CB-839 with capecitabine could serve as an effective treatment for *PIK3CA*-mutant colorectal cancers.

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ABOUT THE COVER

Acquired resistance to EGFR tyrosine kinase inhibitors such as osimertinib involves both EGFR resistance mutations and EGFR-independent mechanisms (e.g., activation of alternate receptor tyrosine kinases). Sun and colleagues reported the discovery of IACS-13909, an allosteric inhibitor of SHP2 that is able to overcome both types of resistance mechanisms in preclinical models. Targeting SHP2 may present a promising strategy to tackle the plasticity and heterogeneity of tyrosine kinase inhibitor resistance. For details, see article by Sun and colleagues on page 4840.



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