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5011 Combined Blockade of IL6 and PD-1/PD-L1 Signaling Abrogates Mutual Regulation of Their Immunosuppressive Effects in the Tumor Microenvironment



Hirotake Tsukamoto, Koji Fujieda, Azusa Miyashita, Satoshi Fukushima, Tokunori Ikeda, Yosuke Kubo, Satoru Senju, Hironobu Ihn, Yasuharu Nishimura, and Hiroyuki Oshiumi

Significance: These findings advance our understanding of IL6-PD1/PD-L1 cross-talk in the tumor microenvironment and provide clues for targeted interventional therapy that may prove more effective against cancer.

5023 Cotargeting Ephrin Receptor Tyrosine Kinases A2 and A3 in Cancer Stem Cells Reduces Growth of Recurrent Glioblastoma

Maleeha A. Qazi, Parvez Vora, Chitra Venugopal, Jarrett Adams, Mohini Singh, Amy Hu, Maryna Gorelik, Minomi K. Subapanditha, Neil Savage, Jiahe Yang, Chirayu Chokshi, Max London, Alexander Gont, David Bobrowski, Natalie Grinshtein, Kevin R. Brown, Naresh K. Murty, Johan Nilvebrant, David Kaplan, Jason Moffat, Sachdev Sidhu, and Sheila K. Singh

Significance: Treatment of rGBM with a novel bispecific-antibody against EPHA2 and EPHA3 reduces tumor burden, paving the way for the development of therapeutic approaches against biologically relevant targets in rGBM.

5038 Oncogenic BRAF^{V600E} Governs Regulatory T-cell Recruitment during Melanoma Tumorigenesis

Tamer B. Shabaneh, Aleksey K. Molodtsov, Shannon M. Steinberg, Peisheng Zhang, Gretel M. Torres, Gadisti A. Mohamed, Andrea Boni, Tyler J. Curiel, Christina V. Angeles, and Mary Jo Turk

Significance: This work provides new insights into the mechanisms by which oncogenic pathways impact immune regulation in the nascent tumor microenvironment.

5050 Microenvironmental Cues Determine Tumor Cell Susceptibility to Neutrophil Cytotoxicity

Maya Gershkovitz, Tanya Fainsod-Levi, Saleh Khawaled, Merav E. Shaul, Ronit V. Sionov, Leonor Cohen-Daniel, Rami I. Aqeilan, Yoav D. Shaul, Zvi G. Fridlender, and Zvi Granot

Significance: EMT is required for metastatic spread and concomitantly enhances tumor cell susceptibility to neutrophil cytotoxicity.

5060 Replication Stress Drives Constitutive Activation of the DNA Damage Response and Radioresistance in Glioblastoma Stem-like Cells



Ross D. Carruthers, Shafiq U. Ahmed, Shaliny Ramachandran, Karen Strathdee, Kathreena M. Kurian, Ann Hedley, Natividad Gomez-Roman, Gabriela Kalna, Mathew Neilson, Lesley Gilmour, Katrina H. Stevenson, Ester M. Hammond, and Anthony J. Chalmers

Significance: These findings shed new light on cancer stem cell biology and reveal novel therapeutics with the potential to improve clinical outcomes by overcoming inherent radioresistance in GBM.

TRANSLATIONAL SCIENCE

5072 A Novel Inhibitor Targets Both Wnt Signaling and ATM/p53 in Colorectal Cancer

Jiongjia Cheng, Mary Dwyer, Karl J. Okolotowicz, Mark Mercola, and John R. Cashman

Significance: These findings identify a potent small molecule that may be therapeutically useful for colon cancer that works by inhibiting Wnt/ β -catenin signaling, activating p53, and binding microtubules without detectable toxicity.

5084 The MDM2/MDMX-p53 Antagonist PM2 Radiosensitizes Wild-Type p53 Tumors



Diana Spiegelberg, Anja C. Mortensen, Sara Lundsten, Christopher J. Brown, David P. Lane, and Marika Nestor

Significance: These findings contribute advances to cancer radiotherapy by utilizing novel p53-reactivating stapled peptides as radiosensitizers in wild-type p53 cancers.

5094 Oligosaccharyltransferase Inhibition Overcomes Therapeutic Resistance to EGFR Tyrosine Kinase Inhibitors

Cecilia Lopez Sambrooks, Marta Baro, Amanda Quijano, Azeet Narayan, Wei Cui, Patricia Greninger, Regina Egan, Abhijit Patel, Cyril H. Benes, W. Mark Saltzman, and Joseph N. Contessa

Significance: EGFR-mutant NSCLC is incurable despite the marked sensitivity of these tumors to EGFR TKIs. These findings identify N-linked glycosylation, a post-translational modification common to EGFR and other oncogenic signaling proteins, as an effective therapeutic target that enhances tumor responses for EGFR-mutant NSCLC.

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- 5107** Normal Breast-Derived Epithelial Cells with Luminal and Intrinsic Subtype-Enriched Gene Expression Document Interindividual Differences in Their Differentiation Cascade
Brijesh Kumar, Mayuri Prasad, Poomima Bhat-Nakshatri, Manjushree Anjanappa, Maitri Kalra, Natascia Marino, Anna Maria Storniololo, Xi Rao, Sheng Liu, Jun Wan, Yunlong Liu, and Harikrishna Nakshatri

Significance: In addition to providing a valuable resource for the breast cancer research community to investigate cell-type origin of different subtypes of breast cancer, this study highlights interindividual differences in normal breast, emphasizing the need to use "normal" cells from multiple sources as controls to decipher the effects of cancer-specific genomic aberrations.

- 5124** Therapeutic Targeting of the Premetastatic Stage in Human Lung-to-Brain Metastasis



Mohini Singh, Chitra Venugopal, Tomas Tokar, Nicole McFarlane, Minomi K. Subapanditha, Maleeha Qazi, David Bakhshinyan, Parvez Vora, Naresh K. Murty, Igor Jurisica, and Sheila K. Singh

Significance: These findings unveil molecular features of the premetastatic stage of lung-to-brain metastases and offer a potential therapeutic strategy to prevent brain metastases.

CONVERGENCE AND TECHNOLOGIES

- 5135** Identification of Metastatic Lymph Nodes in MR Imaging with Faster Region-Based Convolutional Neural Networks



Yun Lu, Qiyue Yu, Yuanxiang Gao, Yunpeng Zhou, Guangwei Liu, Qian Dong, Jinlong Ma, Lei Ding, Hongwei Yao, Zhongtao Zhang, Gang Xiao, Qi An, Guiying Wang, Jinchuan Xi, Weitang Yuan, Yugui Lian, Dianliang Zhang, Chunbo Zhao, Qin Yao, Wei Liu, Xiaoming Zhou, Shuhao Liu, Qingyao Wu, Wenjian Xu, Jianli Zhang, Dongshen Wang, Zhenqing Sun, Yuan Gao, Xianxiang Zhang, Jilin Hu, Maoshen Zhang, Guanrong Wang, Xuefeng Zheng, Lei Wang, Jie Zhao, and Shujian Yang

Significance: Faster R-CNN enables accurate and efficient diagnosis of lymph node metastases.

- 5144** Determination of Tumor Margins with Surgical Specimen Mapping Using Near-Infrared Fluorescence

Rebecca W. Gao, Nutte T. Teraphongphom, Nynke S. van den Berg, Brock A. Martin, Nicholas J. Oberhelman, Vasu Divi, Michael J. Kaplan, Steven S. Hong, Guolan Lu, Robert Ertsey, Willemieke S.F.J. Tummers, Adam J. Gomez, F. Christopher Holsinger, Christina S. Kong, Alexander D. Colevas, Jason M. Warram, and Eben L. Rosenthal

Significance: This study demonstrates that fluorescence can be used as a sensitive and specific method of guiding surgeries for head and neck cancers and potentially other cancers with challenging imaging conditions, increasing the probability of complete resections and improving oncologic outcomes.

- 5155** High-Throughput Screening of Combinatorial Immunotherapies with Patient-Specific *In Silico* Models of Metastatic Colorectal Cancer



Jakob Nikolas Kather, Pornpimol Charoentong, Meggy Suarez-Carmona, Esther Herpel, Fee Klupp, Alexis Ulrich, Martin Schneider, Inka Zoernig, Tom Luedde, Dirk Jaeger, Jan Poleszczuk, and Niels Halama

Significance: This patient-informed in silico tumor growth model allows testing of different cancer treatment strategies and immunotherapies on a cell/tissue level in a clinically relevant scenario.

POPULATION AND PREVENTION SCIENCE

- 5164** A Rare Missense Variant in TCF7L2 Associates with Colorectal Cancer Risk by Interacting with a GWAS-Identified Regulatory Variant in the MYC Enhancer



Jiang Chang, Jianbo Tian, Yang Yang, Rong Zhong, Jiaoyuan Li, Kan Zhai, Juntao Ke, Jiao Lou, Wei Chen, Beibei Zhu, Na Shen, Yi Zhang, Yajie Gong, Ying Zhu, Danyi Zou, Xiating Peng, Kun Huang, and Xiaoping Miao

Significance: Exome-wide association analysis identifies a rare missense variant in TCF7L2 and a common regulatory variant in ATF1 as susceptibility factors of colorectal cancer.

LETTERS TO THE EDITOR

- 5173** CD39 Expression Defines Cell Exhaustion in Tumor-Infiltrating CD8⁺ T Cells—Letter
Martin Thelen, Axel Lechner, Kerstin Wennhold, Michael von Bergwelt-Baildon, and Hans A. Schlößer



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5175 CD39 Expression Defines Cell Exhaustion in Tumor-Infiltrating CD8⁺ T Cells—Response
Fernando P. Canale, María C. Ramello, Nicolás Núñez, Sabrina N. Bossio, Eliane Piaggio, Adriana Gruppi, Eva V. Acosta Rodríguez, and Carolina L. Montes

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Philippe Icard, Ludovic Fournel, Marco Alifano, and Hubert Lincet

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Maria E. Mycielska and Edward K. Geissler

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5183 Editor's Note: Zerumbone Enhances TRAIL-Induced Apoptosis through the Induction of Death Receptors in Human Colon Cancer Cells: Evidence for an Essential Role of Reactive Oxygen Species

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5181 Editor's Note: γ -Tocotrienol Inhibits Pancreatic Tumors and Sensitizes Them to Gemcitabine Treatment by Modulating the Inflammatory Microenvironment

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5185 Retraction: ROS and CHOP Are Critical for Dibenzylideneacetone to Sensitize Tumor Cells to TRAIL through Induction of Death Receptors and Downregulation of Cell Survival Proteins

5186 Retraction: Zerumbone Abolishes RANKL-Induced NF- κ B Activation, Inhibits Osteoclastogenesis, and Suppresses Human Breast Cancer-Induced Bone Loss in Athymic Nude Mice

5187 Retraction: Modification of Cysteine Residue in p65 Subunit of Nuclear Factor- κ B (NF- κ B) by Picroliv Suppresses NF- κ B-Regulated Gene Products and Potentiates Apoptosis

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ABOUT THE COVER

As the most important sensors on cell membrane, G protein-coupled receptors play nonredundant roles in maintaining tumor microenvironment. LGR4, a leucine-rich repeat-containing G-protein coupled receptor, was identified as a novel immune suppressor involved in promoting M2 polarization of tumor-associated macrophages (TAM), which restricts CD8⁺ T-cell-mediated antitumor immune responses. Blockade of LGR4/R-spondin signaling pathway retrieves TAM-mediated immunosuppressive tumor microenvironment, which overcomes resistance of lung cancer and melanoma to the anti-PD-1 therapy, indicating vital roles of Rspo-Lgr4 in host antitumor immunity and a potential therapeutic target in cancer immunotherapy. For details, see article by Tan and colleagues on page 4929.

