

BREAKING INSIGHTS

- 4801** Highlights from Recent Cancer Literature

REVIEW

- 4803** The Effects of Cholesterol-Derived Oncometabolites on Nuclear Receptor Function in Cancer

Sandrine Silvente-Poirot, Florence Dalenc, and Marc Poirot

PERSPECTIVE

- 4809** Does Racial Bias Affect NCI-Funded PIs' Willingness to Mentor Prospective Graduate Students?

Jeffrey D. Robinson, Nathan Dieckmann, Elizabeth Withers, Dena Hassouneh, and Charles R. Thomas Jr

GENOME AND EPIGENOME

- 4812** CircNT5E Acts as a Sponge of miR-422a to Promote Glioblastoma Tumorigenesis



Renjie Wang, Sai Zhang, Xuyi Chen, Nan Li, Jianwei Li, Ruichao Jia, Yuanqing Pan, and Haiqian Liang

Significance: Microarray profiling of circRNA/lncRNA/mRNA in glioblastoma identifies circNT5E as an oncogenic circular RNA and a sponge of miR-422a.

METABOLISM AND CHEMICAL BIOLOGY

- 4826** Interplay between ShcA Signaling and PGC-1 α Triggers Targetable Metabolic Vulnerabilities in Breast Cancer

Young Kyuen Im, Ouafa Najyb, Simon-Pierre Gravel, Shawn McGuirk, Ryuhjin Ahn, Daina Z. Avizonis, Valérie Chénard, Valerie Sabourin, Jesse Hudson, Tony Pawson, Ivan Topisirovic, Michael Pollak, Julie St-Pierre, and Josie Ursini-Siegel

Significance: This study uncovers a previously unrecognized mechanism that links aberrant RTK signaling with metabolic perturbations in breast cancer and exposes metabolic vulnerabilities that can be targeted by inhibitors of oxidative phosphorylation.

MOLECULAR CELL BIOLOGY

- 4839** Erbin Suppresses KSR1-Mediated RAS/RAF Signaling and Tumorigenesis in Colorectal Cancer

Payton D. Stevens, Yang-An Wen, Xiaopeng Xiong, Yekaterina Y. Zaytseva, Austin T. Li, Chi Wang, Ashley T. Stevens, Trevor N. Farmer, Tong Gan, Heidi L. Weiss, Masaki Inagaki, Sylvie Marchetto, Jean-Paul Borg, and Tianyan Gao

Significance: These findings establish the scaffold protein Erbin as a negative regulator of EMT and tumorigenesis in colorectal cancer through direct suppression of Akt and RAS/RAF signaling.

- 4853** Flightless-I Blocks p62-Mediated Recognition of LC3 to Impede Selective Autophagy and Promote Breast Cancer Progression



Jian-Ping He, Pei-Pei Hou, Qi-Tao Chen, Wei-Jia Wang, Xiao-Yu Sun, Peng-Bo Yang, Ying-Ping Li, Lu-Ming Yao, Xiaotong Li, Xin-Dong Jiang, Kun-Yi Chien, Zhi-Ming Zhang, Qiu-Wan Wu, Allison J. Cowin, Qiao Wu, and Hang-Zi Chen

Significance: Flightless-I functions as a checkpoint protein for selective autophagy by interacting with p62 to block its recognition of LC3, leading to tumorigenesis in breast cancer.

- 4865** The Cytochrome P450 Slow Metabolizers CYP2C9*2 and CYP2C9*3 Directly Regulate Tumorigenesis via Reduced Epoxyeicosatrienoic Acid Production

Lindsay N. Sausville, Mahesha H. Gangadhariah, Manuel Chiusa, Shaojun Mei, Shouzu Wei, Roy Zent, James M. Luther, Megan M. Shuey, Jorge H. Capdevila, John R. Falck, F. Peter Guengerich, Scott M. Williams, and Ambra Pozzi

Significance: These findings report single nucleotide polymorphisms in the human CYP2C9 genes, CYP2C9*2 and CYP2C9*3, exert a direct protective role in tumorigenesis by impairing EET biosynthesis.

- 4878** SMAD4 Suppresses WNT-Driven Dedifferentiation and Oncogenesis in the Differentiated Gut Epithelium

Ansu O. Perekatt, Pooja P. Shah, Shannon Cheung, Nidhi Jariwala, Alex Wu, Vishal Gandhi, Namit Kumar, Qiang Feng, Neeket Patel, Lei Chen, Shilpy Joshi, Anbo Zhou, M. Mark Taketo, Jinchuan Xing, Eileen White, Nan Gao, Michael L. Gatz, and Michael P. Verzi

Significance: This work identifies a mechanism through which differentiated cells prevent tumor formation by suppressing oncogenic plasticity.

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TUMOR BIOLOGY AND IMMUNOLOGY

4891



Remission of Spontaneous Canine Tumors after Systemic Cellular Viroimmunotherapy

Teresa Cejalvo, Ana Judith Perisé-Barrios, Isabel del Portillo, Eduardo Laborda, Miguel A. Rodríguez-Milla, Isabel Cubillo, Fernando Vázquez, David Sardón, Manuel Ramirez, Ramon Alemany, Noemí del Castillo, and Javier García-Castro

Significance: The classical clinical limitations of antitumoral viroimmunotherapy can be overcome by use of mesenchymal stem cells.

4902



CTGF Mediates Tumor–Stroma Interactions between Hepatoma Cells and Hepatic Stellate Cells to Accelerate HCC Progression

Yuki Makino, Hayato Hikita, Takahiro Kodama, Minoru Shigekawa, Ryoko Yamada, Ryotaro Sakamori, Hidetoshi Eguchi, Eiichi Morii, Hideki Yokoi, Masashi Mukoyama, Suemizu Hiroshi, Tomohide Tatsumi, and Tetsuo Takehara

Significance: Protumor cross-talk between cancer cells and hepatic stellate cells presents an opportunity for therapeutic intervention against HCC.

4915



Loss of Estrogen-Regulated MIR135A1 at 3p21.1 Promotes Tamoxifen Resistance in Breast Cancer

Wei jie Zhang, Mingming Wu, Qing-Yun Chong, Min Zhang, Xiao Zhang, Lan Hu, Yanghao Zhong, Pengxu Qian, Xiangjun Kong, Sheng Tan, Gaopeng Li, Keshuo Ding, Peter E. Lobie, and Tao Zhu

Significance: Loss of miR-135a in breast cancer disrupts an estrogen receptor-induced negative feedback loop, perpetuating disease progression and resistance to therapy.

4929

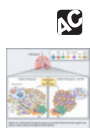


Inhibition of Rspo-Lgr4 Facilitates Checkpoint Blockade Therapy by Switching Macrophage Polarization

Binghe Tan, Xiujuan Shi, Jie Zhang, Juliang Qin, Na Zhang, Hua Ren, Min Qian, Stefan Siwko, Kendra Carmon, Qingyun Liu, Honghui Han, Bing Du, and Mingyao Liu

Significance: This study identifies a novel receptor as a critical switch in TAM polarization whose inhibition sensitizes checkpoint therapy-resistant lung cancer to anti-PD-1 therapy.

4943



Inhaled TLR9 Agonist Renders Lung Tumors Permissive to PD-1 Blockade by Promoting Optimal CD4⁺ and CD8⁺ T-cell Interplay

Marilena Gallotta, Hikmat Assi, Émilie Degagné, Shravan Kumar Kannan, Robert L. Coffman, and Cristiana Guiducci

Significance: These findings demonstrate that local delivery of a toll-like receptor 9 agonist can change the immune content of an entire organ and enhance the efficacy of immune checkpoint inhibition.

4957

IL-6 Mediates Cross-Talk between Tumor Cells and Activated Fibroblasts in the Tumor Microenvironment

Tatiana A. Karakasheva, Eric W. Lin, Qiaosi Tang, Edmund Qiao, Todd J. Waldron, Monica Soni, Andres J. Klein-Szanto, Varun Sahu, Devraj Basu, Shinya Ohashi, Kiichiro Baba, Zachary T. Giaccone, Sarah R. Walker, David A. Frank, E. Paul Wileyto, Qi Long, Margaret C. Dunagin, Arjun Raj, J. Alan Diehl, K.K. Wong, Adam J. Bass, and Anil K. Rustgi

Significance: These findings demonstrate the interaction of esophageal cancer and cancer-associated fibroblasts through IL-6 signaling, providing rationale for a novel therapeutic approach to target these cancers.

4971

Altered Cell-Cycle Control, Inflammation, and Adhesion in High-Risk Persistent Bronchial Dysplasia

Daniel T. Merrick, Michael G. Edwards, Wilbur A. Franklin, Michio Sugita, Robert L. Keith, York E. Miller, Micah B. Friedman, Lori D. Dwyer-Nield, Meredith A. Tennis, Mary C. O'Keefe, Elizabeth J. Donald, Jessica M. Malloy, Adrie van Bokhoven, Storey Wilson, Peter J. Koch, Charlene O'Shea, Christopher Coldren, David J. Orlicky, Xian Lu, Anna E. Baron, Greg Hickey, Timothy C. Kennedy, Roger Powell, Lynn Heasley, Paul A. Bunn, Mark Geraci, and Raphael A. Nemenoff

Significance: Gene expression profiling of high-risk persistent bronchial dysplasia reveals changes in cell-cycle control, inflammatory activity, and epithelial differentiation/cell–cell adhesion that may underlie progression to invasive SCC.

4984

Upregulation of E3 Ubiquitin Ligase CBLC Enhances EGFR Dysregulation and Signaling in Lung Adenocarcinoma

Shiao-Ya Hong, Yu-Rung Kao, Te-Chang Lee, and Cheng-Wen Wu

Significance: This work demonstrates the role of CBLC expression as a diagnostic biomarker and potential therapeutic target in lung adenocarcinoma.

4997

Notch-Induced Myeloid Reprogramming in Spontaneous Pancreatic Ductal Adenocarcinoma by Dual Genetic Targeting

Phyllis F. Cheung, Florian Neff, Christian Neander, Anna Bazarna, Konstantinos Savvatakis, Sven-Thorsten Liffers, Kristina Althoff, Chang-Lung Lee, Everett J. Moding, David G. Kirsch, Dieter Saur, Alexandr V. Bazhin, Marija Trajkovic-Arsic, Mathias F. Heikenwalder, and Jens T. Siveke

Significance: This study provides insight into the role of myeloid-dependent NOTCH signaling in PDAC and accentuates the need to dissect differential roles of signaling pathways in different cellular components within the tumor microenvironment.

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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, Poornima Bhat-Nakshatri, Manjushree Anjanappa, Maitri Kalra, Natascia Marino, Anna Maria Storniollo, 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
- 5176** Extracellular Citrate and Cancer Metabolism—Letter
Philippe Icard, Ludovic Fournel, Marco Alifano, and Hubert Lincet
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Maria E. Mycielska and Edward K. Geissler

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- 5180** Correction: Cofilin Drives Cell-Invasive and Metastatic Responses to TGF- β in Prostate Cancer

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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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- 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.

