

SPECIAL FEATURES

FOCUS ON COMPUTER RESOURCES


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5721 **Discovery of Human-Similar Gene Fusions in Canine Cancers**
Ronan Ulvé, Mélanie Rault, Mathieu Bahin, Laetitia Lagoutte, Jérôme Abadie, Clotilde De Brito, Jean-Michel Coindre, Nadine Botherel, Audrey Rousseau, Valentin Wucher, Edouard Cadieu, Catherine Thieblemont, Christophe Hitte, Laurence Cornevin, Florian Cabillic, Laura Bachelot, David Gilot, Benoit Hennuy, Thierry Guillaudeux, Arnaud Le Goff, Thomas Derrien, Benoit Hédan, and Catherine André

Précis: These findings highlight the utility of integrating spontaneous dog models of cancer in preclinical trials to evaluate targeted therapies.

MOLECULAR AND CELLULAR PATHOBIOLOGY

5728 **miR-193b-Regulated Signaling Networks Serve as Tumor Suppressors in Liposarcoma and Promote Adipogenesis in Adipose-Derived Stem Cells**
Ying Z. Mazzu, Yulan Hu, Rajesh K. Soni, Kelly M. Mojica, Li-Xuan Qin, Phaedra Agius, Zachary M. Waxman, Aleksandra Mihailovic, Nicholas D. Socci, Ronald C. Hendrickson, Thomas Tuschl, and Samuel Singer

Précis: These mechanistic findings reveal critical tyrosine kinase and DNA methylation pathways in liposarcoma, some with immediate implications for therapeutic exploration.

5741 **Upregulation of Cystathionine- β -Synthase in Colonic Epithelia Reprograms Metabolism and Promotes Carcinogenesis**
Ches'Nique M. Phillips, John R. Zatarain, Michael E. Nicholls, Craig Porter, Steve G. Widen, Ketan Thanki, Paul Johnson, Muhammad U. Jawad, Mary P. Moyer, James W. Randall, Judith L. Hellmich, Manjit Maskey, Suimin Qiu, Thomas G. Wood, Nadiya Druzhyna, Bartosz Szczesny, Katalin Módos, Csaba Szabo, Celia Chao, and Mark R. Hellmich

Précis: These findings suggest that efforts to limit transsulfuration pathways that upregulate H2S production may have preventive benefits in limiting colorectal cancer.

5755 **PADI2-Mediated Citrullination Promotes Prostate Cancer Progression**
Lin Wang, Guanhua Song, Xiang Zhang, Tingting Feng, Jihong Pan, Weiwen Chen, Muye Yang, Xinnuo Bai, Yu Pang, Jindan Yu, Jinxiang Han, and Bo Han

Précis: This study reveals protein citrullination, a unique type of protein modification, as a novel pathogenic contributor to advanced prostate cancer, with immediate implications for its potential treatment given the opportunity to reposition modalities currently in clinical development for arthritis therapy.

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- 5769** **YAP Suppresses Lung Squamous Cell Carcinoma Progression via Dereglulation of the DNp63–GPX2 Axis and ROS Accumulation**
Hsinyi Huang, Wenjing Zhang, Yafang Pan, Yijun Gao, Lei Deng, Fuming Li, Fei Li, Xueyan Ma, Shenda Hou, Jing Xu, Peixue Li, Xiaoxun Li, Guohong Hu, Cheng Li, Haiquan Chen, Lei Zhang, and Hongbin Ji
Précis: These findings indicate that the transcription factor YAP, a classic oncogene in lung adenocarcinoma, acts as a tumor suppressor in lung squamous cell carcinoma.

- 5782** **MetaLnc9 Facilitates Lung Cancer Metastasis via a PGK1-Activated AKT/mTOR Pathway**
Tao Yu, Yingjun Zhao, Zhixiang Hu, Jing Li, Dandan Chu, Jiwei Zhang, Zhe Li, Bing Chen, Xiao Zhang, Hongyu Pan, Shengli Li, Hechun Lin, Lei Liu, Mingxia Yan, Xianghuo He, and Ming Yao
Précis: These results establish the long noncoding RNA MetaLnc9 as a driver of metastasis and a candidate therapeutic target for treating advanced NSCLC.

- 5795** **Genetic Dissociation of Glycolysis and the TCA Cycle Affects Neither Normal nor Neoplastic Proliferation**
Laura E. Jackson, Sucheta Kulkarni, Huabo Wang, Jie Lu, James M. Dolezal, Sivakama S. Bharathi, Sarangarajan Ranganathan, Mulchand S. Patel, Rahul Deshpande, Frances Alencastro, Stacy G. Wendell, Eric S. Goetzman, Andrew W. Duncan, and Edward V. Prochownik
Précis: These striking findings show that the pyruvate dehydrogenase complex, which biochemically links glycolysis to the TCA cycle, can be completely eliminated without significantly affecting normal or neoplastic proliferation.

TUMOR AND STEM CELL BIOLOGY

- 5808** **Exosomes from Glioma-Associated Mesenchymal Stem Cells Increase the Tumorigenicity of Glioma Stem-like Cells via Transfer of miR-1587**
Javier Figueroa, Lynette M. Phillips, Tal Shahar, Anwar Hossain, Joy Gumin, Hoon Kim, Andrew J. Bean, George A. Calin, Juan Fueyo, Edgar T. Walters, Raghu Kalluri, Roel G. Verhaak, and Frederick F. Lang
Précis: These results illuminate the mechanism through which glioma-associated mesenchymal stem cells enhance the aggressiveness of glioblastoma.
- 5820** **KIT Suppresses BRAF^{V600E}-Mutant Melanoma by Attenuating Oncogenic RAS/MAPK Signaling**
James V. Neiswender, Robert L. Kortum, Caitlin Bourque, Melissa Kasheta, Leonard I. Zon, Deborah K. Morrison, and Craig J. Ceol
Précis: These findings establish that KIT exerts a negative modifier role in melanoma by attenuating BRAF^{V600E} activity.

- 5831** **ANGPTL1 Interacts with Integrin α 1 β 1 to Suppress HCC Angiogenesis and Metastasis by Inhibiting JAK2/STAT3 Signaling**
Qian Yan, Lingxi Jiang, Ming Liu, Dandan Yu, Yu Zhang, Yan Li, Shuo Fang, Yan Li, Ying-Hui Zhu, Yun-Fei Yuan, and Xin-Yuan Guan
Précis: These results suggest a secreted tumor suppressor has the potential to be developed as a novel prognostic biomarker and novel therapeutic target in liver cancer.

- 5846** **Lysyl Oxidase–like Protein LOXL2 Promotes Lung Metastasis of Breast Cancer**
Fernando Salvador, Alberto Martin, Celia López-Menéndez, Gema Moreno-Bueno, Vanesa Santos, Alberto Vázquez-Naharro, Patricia G. Santamaria, Saleta Morales, Pierre R. Dubus, Laura Muínelo-Romay, Rafael López-López, Jason C. Tung, Valerie M. Weaver, Francisco Portillo, and Amparo Cano
Précis: Conditional transgenic mouse models establish a new role for an ECM regulator in metastatic invasion that is independent of its canonical function in ECM remodeling.

- 5860** **Novel SEC61G–EGFR Fusion Gene in Pediatric Ependymomas Discovered by Clonal Expansion of Stem Cells in Absence of Exogenous Mitogens**
Tiziana Servidei, Daniela Meco, Valentina Muto, Alessandro Bruselles, Andrea Cioffi, Nadia Trivieri, Matteo Lucchini, Roberta Morosetti, Massimiliano Mirabella, Maurizio Martini, Massimo Caldarelli, Anna Lasorella, Marco Tartaglia, and Riccardo Riccardi
Précis: These findings demonstrate how in vitro culture selections applied to genetically heterogeneous tumors that occur rarely may help identify focal mutations that are pharmaceutically actionable in rare cancers, as in the case here for ependymoma, a rare cancer of the central nervous system.

- 5873** **ATG5 Mediates a Positive Feedback Loop between Wnt Signaling and Autophagy in Melanoma**
Abibatou Ndoye, Anna Budina-Kolomets, Curtis H. Kugel III, Marie R. Webster, Amanpreet Kaur, Reeti Behera, Vito W. Rebecca, Ling Li, Patricia A. Brafford, Qin Liu, Y.N. Vashisht Gopal, Michael A. Davies, Gordon B. Mills, Xiaowei Xu, Hong Wu, Meenhard Herlyn, Michael C. Nicastri, Jeffrey D. Winkler, Maria S. Soengas, Ravi K. Amaravadi, Maureen E. Murphy, and Ashani T. Weeraratna
Précis: Restoring β -catenin activity in Wnt5A^{high} melanoma cells sensitizes them to inhibition by the lysosomotropic agent Lys05, a finding of significance as studies to inhibit autophagy move into the clinic.

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5886 FSTL1 Promotes Metastasis and Chemoresistance in Esophageal Squamous Cell Carcinoma through NF κ B–BMP Signaling Cross-talk

Marco Chi-Chung Lau, Kai Yu Ng, Tin Lok Wong, Man Tong, Terence K. Lee, Xiao-Yan Ming, Simon Law, Nikki P. Lee, Annie L. Cheung, Yan-Ru Qin, Kwok Wah Chan, Wen Ning, Xin-Yuan Guan, and Stephanie Ma

Précis: These findings reveal a critical regulator of oncogenesis and metastasis in esophageal squamous cell carcinoma and highlight its potential as a biomarker and therapeutic target.

5900 KDM4 Inhibition Targets Breast Cancer Stem-like Cells



Eric Metzger, Stella S. Stepputtis, Juliane Strietz, Bogdan-Tiberius Preca, Sylvia Urban, Dominica Willmann, Anita Allen, Fides Zenk, Nicola Iovino, Peter Bronsert, Amelie Proske, Marie Follo, Melanie Boerries, Elmar Stickeler, Jiangchun Xu, Michael B. Wallace, Jeffrey A. Stafford, Toufike Kanouni, Jochen Maurer, and Roland Schüle

Précis: Breast cancer stem-like cells that can recapitulate triple-negative breast tumors were used in this study to help validate therapeutic targets such as the epigenetic regulator KDM4.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

5913 MCT1 Inhibitor AZD3965 Increases Mitochondrial Metabolism, Facilitating Combination Therapy and Noninvasive Magnetic Resonance Spectroscopy



Mounia Belouèche-Babari, Slawomir Wantuch, Teresa Casals Galobart, Markella Koniordou, Harold G. Parkes, Vaitha Arunan, Yuen-Li Chung, Thomas R. Eykyn, Paul D. Smith, and Martin O. Leach

Précis: These findings show how blocking the lactate transporter MCT1 rewires metabolism to enable tumor cell survival under therapeutic challenge.

5925 Caveolae-Mediated Endocytosis Is Critical for Albumin Cellular Uptake and Response to Albumin-Bound Chemotherapy

Moumita Chatterjee, Edgar Ben-Josef, Ryan Robb, Marall Vedaie, Star Seum, Krishnan Thirumoorthy, Kamalakannan Palanichamy, Matthew Harbrecht, Arnab Chakravarti, and Terence M. Williams

Précis: These findings define a key lipid raft-bound plasma membrane scaffolding protein as a predictive biomarker for the response to albumin-conjugated cancer drugs, such as the widely used antimitotic agent Abraxane.

5938 Tethering IL2 to Its Receptor IL2R β Enhances Antitumor Activity and Expansion of Natural Killer NK92 Cells

Youssef Jounaidi, Joseph F. Cotten, Keith W. Miller, and Stuart A. Forman

Précis: These findings describe a strategy to improve natural killer cells as a cellular immunotherapy for cancer by engineering them to express a fusion protein that tethers interleukin-2 to its receptor IL2R β .

MICROENVIRONMENT AND IMMUNOLOGY

5952 Gemcitabine-Induced TIMP1 Attenuates Therapy Response and Promotes Tumor Growth and Liver Metastasis in Pancreatic Cancer

Zenobia D'Costa, Keaton Jones, Abul Azad, Ruud van Stiphout, Su Y. Lim, Ana L. Gomes, Paul Kinchesh, Sean C. Smart, W. Gillies McKenna, Francesca M. Buffa, Owen J. Sansom, Ruth J. Muschel, Eric O'Neill, and Emmanouil Fokas

Précis: These findings suggest TIMP1 as an appealing therapeutic target in pancreatic cancer, which continues to defy effective treatment.

5963 Enhanced Acid Sphingomyelinase Activity Drives Immune Evasion and Tumor Growth in Non-Small Cell Lung Carcinoma

Katerina Kachler, Maximilian Bailer, Lisanne Heim, Fabian Schumacher, Martin Reichel, Corinna D. Holzinger, Sonja Trump, Susanne Mittler, Juliana Monti, Denis I. Trufa, Ralf J. Rieker, Arndt Hartmann, Horia Sirbu, Burkhard Kleuser, Johannes Kornhuber, and Susetta Finotto

Précis: An enzyme that controls membrane composition and dynamics in cancer cells is a potential therapeutic target for immunomodulatory therapy in lung adenocarcinoma.

5977 Tenascin-C and Integrin α 9 Mediate Interactions of Prostate Cancer with the Bone Microenvironment

Rebeca San Martin, Ravi Pathak, Antrix Jain, Sung Yun Jung, Susan G. Hilsenbeck, María C. Piña-Barba, Andrew G. Sikora, Kenneth J. Pienta, and David R. Rowley

Précis: This study identifies fundamental mechanisms of metastasis through the use of novel models of this process.

5989 Anti-CD137 Suppresses Tumor Growth by Blocking Reverse Signaling by CD137 Ligand

Sang W. Kang, Sang C. Lee, So H. Park, Juyang Kim, Hyeon H. Kim, Hyeon-Woo Lee, Su K. Seo, Byoung S. Kwon, Hong R. Cho, and Byungsuk Kwon

Précis: This potentially seminal study suggests a nodal role for CD137-CD137L immune signaling in the coordinate control of tumor immunosurveillance, spotlighting CD137L as an attractive intervention point to enhance cancer immunotherapy.

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6001 Transplantation of iPS-Derived Tumor Cells with a Homozygous MHC Haplotype Induces GRP94 Antibody Production in MHC-Matched Macaques

Hirohito Ishigaki, Toshinaga Maeda, Hirokazu Inoue, Tsuyoshi Akagi, Takako Sasamura, Hideaki Ishida, Toshiro Inubushi, Junko Okahara, Takashi Shiina, Misako Nakayama, Yasushi Itoh, and Kazumasa Ogasawara

Précis: These seminal findings show that adequate immune surveillance depends vitally on the generation of cancer-specific antibodies.

INTEGRATED SYSTEMS AND TECHNOLOGIES

6011 Optical Coherence Tomography Detects Necrotic Regions and Volumetrically Quantifies Multicellular Tumor Spheroids

Yongyang Huang, Shunqiang Wang, Qiongyu Guo, Sarah Kessel, Ian Rubinoff, Leo Li-Ying Chan, Peter Li, Yaling Liu, Jean Qiu, and Chao Zhou

Précis: These findings introduce a label-free imaging technology capable of performing live, longitudinal analysis of 3D tumor spheroids for high-throughput screening of anticancer drugs.

6021 Chemotherapy-Induced Macrophage Infiltration into Tumors Enhances Nanographene-Based Photodynamic Therapy

Yang Zhao, Chenran Zhang, Liquan Gao, Xinhe Yu, Jianhao Lai, Dehua Lu, Rui Bao, Yanpu Wang, Bing Jia, Fan Wang, and Zhaofei Liu

Précis: Photodynamic therapy after chemotherapy is a promising cancer treatment strategy, with macrophage-specific molecular imaging an important potential aid in the rational design of combination therapies.

PREVENTION AND EPIDEMIOLOGY

6033 Diabetes Treatments and Risks of Adverse Breast Cancer Outcomes among Early-Stage Breast Cancer Patients: A SEER-Medicare Analysis

Lu Chen, Jessica Chubak, Denise M. Boudreau, William E. Barlow, Noel S. Weiss, and Christopher I. Li

Précis: A retrospect cohort of 14,766 women with stage I/II breast cancer suggests that metformin may be a preferred treatment for diabetes among women with breast cancer.

LETTER TO THE EDITOR

6042 Cross-Cancer Analysis Reveals Novel Pleiotropic Associations—Letter

Lei Quan, Alan Hutson, and Peter Demant

6045 Cross-Cancer Analysis Reveals Novel Pleiotropic Associations—Response

Rayjean J. Hung, Gordon Fehring, Graham Casey, Stephen B. Gruber, Ulrike Peters, Ellen L. Goode, Thomas A. Sellers, Christopher A. Haiman, David J. Hunter, Peter Kraft, Christopher I. Amos, Matthew L. Freedman, and Michael D. Wilson

CORRECTIONS

6047 Correction: SSRP1 Cooperates with PARP and XRCC1 to Facilitate Single-Strand DNA Break Repair by Chromatin Priming

6048 Correction: A Squalene-Based Nanomedicine for Oral Treatment of Colon Cancer

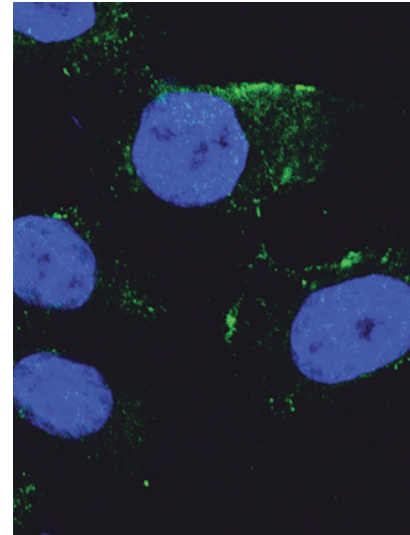
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ABOUT THE COVER

Albumin-bound/conjugated chemotherapies such as nab-paclitaxel (Abraxane) are a class of chemotherapies that have shown improvements over conventional chemotherapy in certain tumor types, resulting in reduced toxicity and/or increased efficacy. The improved targeting to tumor cells is thought to be in part due to an enhanced permeability and retention effect within tumors, but no useful molecular biomarkers exist to predict efficacy to this class of drugs. Caveolae are flask-shaped invaginations of the plasma membrane that appear important for albumin uptake, and caveolin-1 is the protein required for caveolae formation. Using immunofluorescence, it was found that the degree of caveolin-1 expression dictates uptake of nab-paclitaxel, as visualized by immunofluorescence for albumin (green) in DAPI-stained (blue) tumor cells. For details, see article by Chatterjee and colleagues on page 5925.



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