

BREAKING ADVANCES

- 4205** Highlights from Recent Cancer Literature

MOLECULAR AND CELLULAR PATHOBIOLOGY

- 4207** Micronuclei Frequency in Tumors Is a Predictive Biomarker for Genetic Instability and Sensitivity to the DNA Repair Inhibitor AsidNA

Wael Jdey, Sylvain Thierry, Tatiana Popova, Marc-Henri Stern, and Marie Dutreix

Précis: Biomarkers of genetic instability can be used on patient biopsies for better characterization of tumor specificities in view to improve precision medicine.

- 4217** Smurf2-Mediated Stabilization of DNA Topoisomerase II α Controls Genomic Integrity

Andrea Emanuelli, Aurora P. Borroni, Liat Apel-Sarid, Pooja A. Shah, Dhanoop Manikoth Ayyathan, Praveen Koganti, Gal Levy-Cohen, and Michael Blank

Précis: These findings illuminate how the stability of DNA topoisomerase II α is controlled in cells, with implications for understanding this enzyme in chromosome inheritance and as a target of several important anticancer drugs.

- 4228** Acetylation of Mastermind-like 1 by p300 Drives the Recruitment of NACK to Initiate Notch-Dependent Transcription



Ke Jin, Wen Zhou, Xiaoqing Han, Zhiqiang Wang, Bin Li, Shawn Jeffries, Wensi Tao, David J. Robbins, and Anthony J. Capobianco

Précis: These findings provide new insight for Notch signaling and a potential therapeutic strategy for Notch-dependent cancer.

- 4238** Utility of Genomic Analysis In Circulating Tumor DNA from Patients with Carcinoma of Unknown Primary



Shumei Kato, Nithya Krishnamurthy, Kimberly C. Banks, Pradip De, Kirstin Williams, Casey Williams, Brian Leyland-Jones, Scott M. Lippman, Richard B. Lanman, and Razelle Kurzrock

Précis: Deep sequencing of carcinomas of unknown origin can identify patients with pharmacologically actionable alterations, justifying the inclusion of noninvasive liquid biopsies in next-generation clinical trials.

- 4247** RGS12 Is a Novel Tumor-Suppressor Gene in African American Prostate Cancer That Represses AKT and MNX1 Expression

Yongquan Wang, Jianghua Wang, Li Zhang, Omer Faruk Karatas, Longjiang Shao, Yiqun Zhang, Patricia Castro, Chad J. Creighton, and Michael Ittmann

Précis: These findings identify RGS12 as a novel tumor suppressor gene in prostate cancer in African Americans, which may serve as an important prognostic marker and therapeutic target.

- 4258** Unpaired Extracellular Cysteine Mutations of CSF3R Mediate Gain or Loss of Function

Haijiao Zhang, Sophie Means, Anna Reister Schultz, Kevin Watanabe-Smith, Bruno C. Medeiros, Daniel Bottomly, Beth Wilmot, Shannon K. McWeeney, Tim Kükenshöner, Oliver Hantschel, and Jeffrey W. Tyner

Précis: These findings demonstrate the structural and functional importance of conserved extracellular cysteine pairs in CSF3R, a gene possibly mutated frequently in leukemias, and suggesting the possibility of cysteine-mediated gain- and loss-of-function mutations in other oncogenic receptors.

TUMOR AND STEM CELL BIOLOGY

- 4268** EIF1AX and NRAS Mutations Co-occur and Cooperate in Low-Grade Serous Ovarian Carcinomas

Dariusz Etamadmoghadam, Walid J. Azar, Ying Lei, Tania Moujabber, Dale W. Garsed, Catherine J. Kennedy, Sian Fereday, Chris Mitchell, Yoke-Eng Chiew, Joy Hendley, Raghwa Sharma, Paul R. Harnett, Jason Li, Elizabeth L. Christie, Ann-Marie Patch, Joshy George, George Au-Yeung, Gisela Mir Arnau, Timothy P. Holloway, Timothy Semple, John V. Pearson, Nicola Waddell, Sean M. Grimmond, Martin Köbel, Helen Rizos, Ivan B. Lomakin, David D.L. Bowtell, and Anna deFazio for The Australian Ovarian Cancer Study Group

Précis: These findings represent a new treatment target for patients with NRAS-mutated cancer.

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- 4279** **Phosphoproteomic Profiling Reveals ALK and MET as Novel Actionable Targets across Synovial Sarcoma Subtypes**
 Emmy D.G. Fleuren, Myrella Vlenterie, Winette T.A. van der Graaf, Melissa H.S. Hillebrandt-Roeffen, James Blackburn, Xiuquan Ma, Howard Chan, Mandy C. Magias, Anke van Erp, Laurens van Houdt, Sabri A.S. Cebeci, Amy van de Ven, Uta E. Flucke, Erin E. Heyer, David M. Thomas, Christopher J. Lord, Kieren D. Marini, Vijesh Vaghjiani, Tim R. Mercer, Jason E. Cain, Jianmin Wu, Yvonne M.H. Versleijen-Jonkers, and Roger J. Daly
Précis: These findings couple global profiling functional validation using both in vitro and in vivo models of sarcoma, revealing novel therapeutic targets in synovial sarcomas.
- 4293** **Targeting SRC Coactivators Blocks the Tumor-Initiating Capacity of Cancer Stem-like Cells**
Aarti D. Rohira, Fei Yan, Lei Wang, Jin Wang, Suoling Zhou, Andrew Lu, Yang Yu, Jianming Xu, David M. Lonard, and Bert W. O'Malley
Précis: SRC-3 participates in the creation and maintenance of a stem-like state that can be targeted with a small-molecule inhibitor for SRC-3/SRC-1 function.
- 4305** **Hypoxia-Induced Downregulation of DUSP-2 Phosphatase Drives Colon Cancer Stemness**
Pei-Chi Hou, Yo-Hua Li, Shih-Chieh Lin, Shau-Chieh Lin, Jenq-Chang Lee, Bo-Wen Lin, Jing-Ping Liou, Jang-Yang Chang, Ching-Chuan Kuo, Yi-Min Liu, H. Sunny Sun, and Shaw-Jenq Tsai
Précis: This study shows how COX-2 becomes upregulated in cancer cells, where it promotes stemness properties and drug resistance, and it also defines HDAC inhibitors that can ameliorate these effects.
- 4317** **Loss of FAM46C Promotes Cell Survival in Myeloma**
Yuan Xiao Zhu, Chang-Xin Shi, Laura A. Bruins, Patrick Jedlowski, Xuwei Wang, K. Martin Kortüm, Moulun Luo, Jonathan M. Ahmann, Esteban Braggio, and A. Keith Stewart
Précis: These findings demonstrate that a highly mutated gene in multiple myeloma promotes cell survival when its expression or function is compromised, suggesting a key role in development of this aggressive cancer.
- 4328** **Fructose-1,6-bisphosphatase Inhibits ERK Activation and Bypasses Gemcitabine Resistance in Pancreatic Cancer by Blocking IQGAP1–MAPK Interaction**
Xin Jin, Yunqian Pan, Liguang Wang, Tao Ma, Lizhi Zhang, Amy H. Tang, Daniel D. Billadeau, Heshui Wu, and Haojie Huang
Précis: These findings identify FBP1 as a critical tumor suppressor and show that mimicking its activity with a small peptide inhibitor may provide an effective strategy to eradicate pancreatic cancer cells.
- 4342** **Inhibiting p53 Acetylation Reduces Cancer Chemotoxicity**
 Shunsheng Zheng, Xin Yu Koh, Hui Chin Goh, Siti Aishah B. Rahmat, Le-Ann Hwang, and David P. Lane
Précis: These findings suggest how a brief and reversible inhibition of p53 acetylation could potentially improve chemotherapy outcomes.
- 4355** **Glucose Catabolism in Liver Tumors Induced by c-MYC Can Be Sustained by Various PKM1/PKM2 Ratios and Pyruvate Kinase Activities**
 Andrés Méndez-Lucas, Xiaolei Li, Junjie Hu, Li Che, Xinhua Song, Jiaoyuan Jia, Jingxiao Wang, Chencheng Xie, Paul C. Driscoll, Darjus F. Tschaharganeh, Diego F. Calvisi, Mariia Yuneva, and Xin Chen
Précis: Increased PKM2 expression is not required for c-Myc-induced liver tumor formation, suggesting that targeting PKM2 may have limited therapeutic value for treatment of liver cancers.
- 4365** **Infection Exposure Promotes ETV6-RUNX1 Precursor B-cell Leukemia via Impaired H3K4 Demethylases**
 Guillermo Rodríguez-Hernández, Julia Hauer, Alberto Martín-Lorenzo, Daniel Schäfer, Christoph Bartenhagen, Idoia García-Ramírez, Franziska Auer, Inés González-Herrero, Lucía Ruiz-Roca, Michael Gombert, Vera Okpanyi, Ute Fischer, Cai Chen, Martín Dugas, Sanil Bhatia, René Martin Linka, Marta García-Suquia, María Victoria Rascón-Trincado, Angel García-Sánchez, Oscar Blanco, María Begoña García-Cenador, Francisco Javier García-Criado, César Cobaleda, Diego Alonso-López, Javier De Las Rivas, Markus Müschen, Carolina Vicente-Dueñas, Isidro Sánchez-García, and Arndt Borkhardt
Précis: Impaired epigenetic regulation and high RAG expression provides a genetic basis for why only a small fraction of patients with multiple oncogenic mutations in pre-leukemic clones develop precursor B cell acute lymphocytic leukemia.

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THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

- 4378** **Characterization of MK-4166, a Clinical Agonistic Antibody That Targets Human GITR and Inhibits the Generation and Suppressive Effects of T Regulatory Cells**
 Selvakumar Sukumar, Douglas C. Wilson, Ying Yu, Jerelyn Wong, Saraswathi Naravula, Grigori Ermakov, Romina Riener, Bhagyashree Bhagwat, Antoaneta S. Necheva, Jeff Grein, Tatyana Churakova, Ruban Mangadu, Peter Georgiev, Denise Manfra, Elaine M. Pinheiro, Venkataraman Sriram, Wendy J. Bailey, Danuta Herzyk, Terrill K. McClanahan, Aaron Willingham, Amy M. Beebe, and Svetlana Sadekova
Précis: This study presents a preclinical proof of concept demonstrating the anticancer utility of a humanized monoclonal antibody against GITR, an important co-stimulatory receptor on T cells, which can be agonized to reverse immune suppression in the treatment of cancer.
- 4389** **Normal and Malignant Cells Exhibit Differential Responses to Calcium Electroporation**
Stine K. Frandsen, Mie B. Krüger, Uma M. Mangalanathan, Trine Tramm, Faisal Mahmood, Ivana Novak, and Julie Gehl
Précis: Reduced plasma membrane calcium ATPase protein levels render tumor cells sensitive to calcium electroporation-induced necrosis, with limited effects on normal tissues, suggesting that calcium electroporation may offer a simple generalized tool for eradication of solid tumors.
- 4402** **A Genome-Wide CRISPR Screen Identifies Genes Critical for Resistance to FLT3 Inhibitor AC220**
Panpan Hou, Chao Wu, Yuchen Wang, Rui Qi, Dheeraj Bhavanesi, Zhixiang Zuo, Cedric Dos Santos, Shuliang Chen, Yu Chen, Hong Zheng, Hong Wang, Alexander Perl, Deyin Guo, and Jian Huang
Précis: These findings identify mechanisms of drug resistance in AML cells and discover a number of genes whose ablation confers drug resistance to a potential drug.
- 4414** **MCAM Mediates Chemoresistance in Small-Cell Lung Cancer via the PI3K/AKT/SOX2 Signaling Pathway**
Satyendra C. Tripathi, Johannes F. Fahrman, Muge Celik, Mitzi Aguilar, Kieren D. Marini, Mohit K. Jolly, Hiroyuki Katayama, Hong Wang, Eunice N. Murage, Jennifer B. Dennison, D. Neil Watkins, Herbert Levine, Edwin J. Ostrin, Ayumu Taguchi, and Samir M. Hanash
Précis: This study suggests an approach to sensitize small-cell lung cancers to chemotherapy, highlighting a specific candidate target for therapeutic intervention.
- 4426** **Amlexanox Downregulates S100A6 to Sensitize KMT2A/AFF1-Positive Acute Lymphoblastic Leukemia to TNF α Treatment**
Hayato Tamai, Hiroki Yamaguchi, Koichi Miyake, Miyuki Takatori, Tomoaki Kitano, Satoshi Yamanaka, Syunsuke Yui, Keiko Fukunaga, Kazutaka Nakayama, and Koiti Inokuchi
Précis: This study shows how repositioning an approved allergy drug can undercut immune escape and enhance graft-versus-leukemia effects of stem cell transplants in preclinical models of an acute form of pediatric leukemia, providing a mechanistic rationale for immediate clinical testing in this setting.
- 4434** **Targeting Vascular Endothelial-Cadherin in Tumor-Associated Blood Vessels Promotes T-cell-Mediated Immunotherapy**
Yang Zhao, Ka Ka Ting, Jia Li, Victoria C. Cogger, Jinbiao Chen, Anna Johansson-Percival, Shin Foong Ngiow, Jeff Holst, Georges Grau, Shom Goel, Thorleif Muller, Elisabetta Dejana, Geoff McCaughan, Mark J. Smyth, Ruth Ganss, Mathew A. Vadas, and Jennifer R. Gamble
Précis: These findings identify the miR-27/VE-cadherin interaction as a verified target to improve immunotherapy via stabilization of VE-cadherin levels in solid tumor vasculature.
- 4448** **GLI1 Blockade Potentiates the Antitumor Activity of PI3K Antagonists in Lung Squamous Cell Carcinoma**
Sahba Kasiri, Chunli Shao, Baozhi Chen, Alexandra N. Wilson, Paul Yenerall, Brenda C. Timmons, Luc Girard, Hui Tian, Carmen Behrens, Ignacio I. Wistuba, Adi F. Gazdar, and James Kim
Précis: Combined targeting of the PI3K-mTOR pathway and the transcription factor GLI1 may improve outcomes in PI3K pathway-driven lung cancers, providing an opportunity to address the failure of PI3K antagonists as effective monotherapies.
- 4460** **Posttranscriptional Upregulation of IDH1 by HuR Establishes a Powerful Survival Phenotype in Pancreatic Cancer Cells**
Mahsa Zarei, Shruti Lal, Seth J. Parker, Avinoam Nevler, Ali Vaziri-Gohar, Katerina Dukleska, Nicole C. Mambelli-Lisboa, Cynthia Moffat, Fernando F. Blanco, Saswati N. Chand, Masaya Jimbo, Joseph A. Cozzitorto, Wei Jiang, Charles J. Yeo, Eric R. Londin, Erin L. Seifert, Christian M. Metallo, Jonathan R. Brody, and Jordan M. Winter
Précis: This important study highlights the HuR-IDH1 regulatory axis as a critical, actionable therapeutic target in pancreatic cancer.

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MICROENVIRONMENT AND IMMUNOLOGY

- 4472** Heme-oxygenase-1 Production by Intestinal CX3CR1⁺ Macrophages Helps to Resolve Inflammation and Prevents Carcinogenesis
Giulia Marelli, Marco Erreni, Achille Anselmo, Valentina Taverniti, Simone Guglielmetti, Alberto Mantovani, and Paola Allavena
Précis: These findings demonstrate how colon-resident CX3CR1⁺ macrophages help prevent the establishment of chronic inflammation and cancer by producing HMOX-1.

- 4486** NF1^{+/-} Hematopoietic Cells Accelerate Malignant Peripheral Nerve Sheath Tumor Development without Altering Chemotherapy Response
Rebecca D. Dodd, Chang-Lung Lee, Tess Overton, Wesley Huang, William C. Eward, Lixia Luo, Yan Ma, Davis R. Ingram, Keila E. Torres, Diana M. Cardona, Alexander J. Lazar, and David G. Kirsch
Précis: Mouse models demonstrate how the genetics of myeloid cells in the tumor microenvironment influence the biology of a type of pediatric tumor of the connective tissues that surround nerves, with potential clinical implications.

INTEGRATED SYSTEMS AND TECHNOLOGIES

- 4498** MET Exon 14 Mutation Encodes an Actionable Therapeutic Target in Lung Adenocarcinoma
Xinyuan Lu, Nir Peled, John Greer, Wei Wu, Peter Choi, Alice H. Berger, Sergio Wong, Kuang-Yu Jen, Youngho Seo, Byron Hann, Angela Brooks, Matthew Meyerson, and Eric A. Collisson
Précis: MET exon 14-skipping mutations are relatively common in NSCLC, encoding an active and druggable target and genomically evolving to overcome therapeutic targeting.

- 4506** Raman-Encoded Molecular Imaging with Topically Applied SERS Nanoparticles for Intraoperative Guidance of Lumpectomy
Yu "Winston" Wang, Nicholas P. Reeder, Soyoung Kang, Adam K. Glaser, Qian Yang, Matthew A. Wall, Sara H. Javid, Suzanne M. Dintzis, and Jonathan T.C. Liu
Précis: This study introduces a novel noninvasive imaging technique that can rapidly detect positive surgical margins with high sensitivity and specificity in breast carcinoma.

CLINICAL STUDIES

- 4517** Functionally Null RAD51D Missense Mutation Associates Strongly with Ovarian Carcinoma
Barbara Rivera, Massimo Di Iorio, Jessica Frankum, Javad Nadaf, Somayyeh Fahiminiya, Suzanna L. Arcand, David L. Burk, Damien Grapton, Eva Tomiak, Valerie Hastings, Nancy Hamel, Rabea Wagener, Olga Aleynikova, Sylvie Giroux, Fadi F. Hamdan, Alexandre Dionne-Laporte, George Zogopoulos, Francois Rousseau, Albert M. Berghuis, Diane Provencher, Guy A. Rouleau, Jacques L. Michaud, Anne-Marie Mes-Masson, Jacek Majewski, Susanne Bens, Reiner Siebert, Steven A. Narod, Mohammad R. Akbari, Christopher J. Lord, Patricia N. Tonin, Alexandre Orthwein, and William D. Foulkes
Précis: Carriers of a pathogenic missense mutation in the gene encoding the DNA repair protein RAD51D are at higher risk for ovarian cancer that may respond favorably to PARP inhibitor therapy.

- 4530** Quantitative Whole Genome Sequencing of Circulating Tumor Cells Enables Personalized Combination Therapy of Metastatic Cancer
Natali Gulbahce, Mark Jesus M. Magbanua, Robert Chin, Misha R. Agarwal, Xuhao Luo, Jia Liu, Daniel M. Hayden, Qing Mao, Serban Ciotlos, Zhenyu Li, Yanxiang Chen, Xingpeng Chen, Yuxiang Li, Rebecca Yu Zhang, Katharine Lee, Rick Tearle, Emily Park, Snezana Drmanac, Hope S. Rugo, John W. Park, Radoje Drmanac, and Brock A. Peters
Précis: These findings demonstrate the feasibility of generating high quality whole genome data from a small number of circulating tumor cells and show that this information can be extremely informative for personalized therapy.



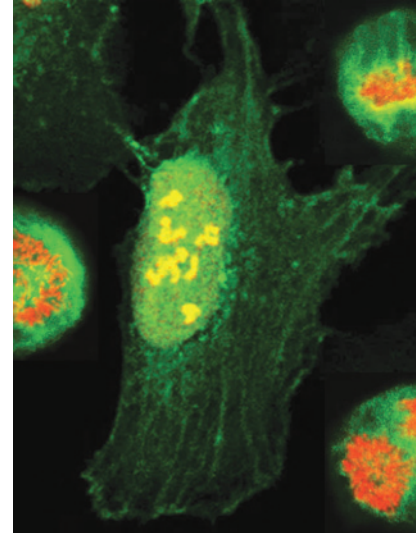
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ABOUT THE COVER

DNA topoisomerase IIa (Topo IIa) plays a pivotal role in chromatin organization and unaltered chromosome inheritance. Moreover, Topo IIa is a core target of several anticancer drugs. Smurf2, an E3 ubiquitin ligase and suggested tumor suppressor, acts as a key cellular factor that directly binds and stabilizes Topo IIa and prevents the formation of pathological chromatin bridges. The image shows molecular biodistribution of Smurf2 and Topo IIa in human interphase and mitotic cells. For details, see article by Emanuelli and colleagues on page 4217.



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