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## 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 Idey, 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 IIA Controls Genomic Integrity  
Andrea Emanuelli, Aurora P. Borroni, Liat Apel-Sand, Pooja A. Shah, Dhanoop Manikoth Ayyathan, Praveen Koganti, Gal Levy-Cohen, and Michael Blank  
Précis: These findings illuminate how the stability of DNA topoisomerase IIA 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, Xiaoying 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  
Shumel 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.

## Tumor and Stem Cell Biology

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.

4268 EIF1AX and NRAS Mutations Co-occur and Cooperate in Low-Grade Serous Ovarian Carcinomas  
Précis: These findings identify EIF1AX and NRAS mutations as significant co-mutations in low-grade serous ovarian carcinomas and suggest potential therapeutic targets.

## References

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4279 Phosphoproteomic Profiling Reveals ALK and MET as Novel Actionable Targets across Synovial Sarcoma Subtypes

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

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, Liguo Wang, Tao Ma, Lizi 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. Tsahanganeh, Diego F. Calvisi, Marisa Yunvea, 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

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.
MCAM Mediates Chemoresistance in Small-Cell Lung Cancer via the P3K/akt/sox2 Signaling Pathway


Précis: This study suggests an approach to sensitize small-cell lung cancers to chemotherapy, highlighting a specific candidate target for therapeutic intervention.

GLI1 Blockade Potentiates the Antitumor Activity of PI3K Antagonists in Lung Squamous Cell Carcinoma

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.

Posttranscriptional Upregulation of IDH1 by HuR Establishes a Powerful Survival Phenotype in Pancreatic Cancer Cells


Précis: This important study highlights the HuR–IDH1 regulatory axis as a critical, actionable therapeutic target in pancreatic cancer.

Amlexanox Downregulates S100A6 to Sensitize KMT2A/aff1-Positive Acute Lymphoblastic Leukemia to TNFα 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.

Targeting Vascular Endothelial-Cadherin in Tumor-Associated Blood Vessels Promotes T-cell–Mediated Immunotherapy

Yang Zhao, Ka K. Ting, Jia Li, Victoria C. Cogger, Jinbiao Chen, Anna Johannsson-Percival, Shin Foong Ngioi, 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.

Characterization of MK-4166, a Clinical Agonistic Antibody That Targets Human Gitr and Inhibits the Generation and Suppressive Effects of T Regulatory Cells


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.

Normal and Malignant Cells Exhibit Differential Responses to Calcium Electroporation

Stine K. Frandsen, Mie B. Kruger, Ilma M. Mangalanathan, Trine Tramm, Faisal Mahmood, Ivana Novak, and Julie Goh

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.

A Genome-Wide Crispr Screen Identifies Genes Critical for Resistance to Fli3 Inhibitor Ac220

Panpan Hou, Chao Wu, Yuchen Wang, Rui Qi, Dheeraj Bhavanasi, Zhixiang Zuo, Cedric Dos Santos, Shuliang Chen, Yu Chen, Hong Zheng, Hong Wang, Alexander Perl, Dejin 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.

Posttranscriptional Upregulation of Idh1 by Huir Establishes a Powerful Survival Phenotype in Pancreatic Cancer Cells


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.

CLINICAL STUDIES

4517 Functionally Null RAD51D Missense Mutation Associates Strongly with Ovarian Carcinoma
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.

INTEGRATED SYSTEMS AND TECHNOLOGIES

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. Kisch
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.

4506 Raman-Encoded Molecular Imaging with Topically Applied SERS Nanoparticles for Intraoperative Guidance of Lumpectomy
Yu "Winston" Wang, Nicholas P. Reder, 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.

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.

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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.