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Stine E. Weis-Banke, Mads Lerdrup, Daniela Kleine-Kohlbrecher, Faizaan Mohammad, Simone Sidoli, Ole N. Jensen, Toshihiko Yanase, Tomoko Nakamura, Akira Iwase, Anthe Stylianou, Nadeem R. Abu-Rustum, Carol Aghajanian, Robert Soslow, Arnaud Da Cruz Paula, Richard P. Koche, Britta Weigelt, Jesper Christensen, Kristian Helin, and Paul A.C. Cloos
FOXL2^{C134W} hijacks SMAD4 and leads to the expression of genes involved in EMT, stemness, and oncogenesis in AGCT, making FOXL2^{C134W} and the TGFβ pathway therapeutic targets in this condition.

- 3480** **The Pathognomonic FOXL2 C134W Mutation Alters DNA-Binding Specificity**
Annaïck Carles, Genny Trigo-Gonzalez, Qi Cao, S.-W. Grace Cheng, Michelle Moksa, Misha Bilenky, David G. Huntsman, Gregg B. Morin, and Martin Hirst
A mechanistic understanding of FOXL2^{C134W}-induced regulatory state alterations drives discovery of a rationally designed therapeutic strategy.

METABOLISM AND CHEMICAL BIOLOGY

- 3492** **Nitrogen Trapping as a Therapeutic Strategy in Tumors with Mitochondrial Dysfunction**
Hanumantha Rao Madala, Iiro Taneli Helenius, Wen Zhou, Evanna Mills, Yiyun Zhang, Yan Liu, Ana M. Metelo, Michelle L. Kelley, Surendra Punganuru, Kyung Bo Kim, Benjamin Olenchock, Eugene Rhee, Andrew M. Intlekofer, Othon Iliopoulos, Edward Chouchani, and Jing-Ruey Joanna Yeh
These findings demonstrate that OXPHOS deficiency caused by either hypoxia or mutations, which can significantly increase cancer virulence, renders tumors sensitive to aKG esters by targeting their dependence upon GOT1 for aspartate synthesis.

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3507 Bromodomain-Selective BET Inhibitors Are Potent Antitumor Agents against MYC-Driven Pediatric Cancer

P. Jake Slavish, Liying Chi, Mi-Kyung Yun, Lyudmila Tsurkan, Nancy E. Martinez, Barbara Jonchere, Sergio C. Chai, Michele Connelly, M. Brett Waddell, Sourav Das, Geoffrey Neale, Zhenmei Li, William R. Shadrack, Rachelle R. Olsen, Kevin W. Freeman, Jonathan A. Low, Jeanine E. Price, Brandon M. Young, Nagakumar Bharatham, Vincent A. Boyd, Jun Yang, Richard E. Lee, Marie Morfouace, Martine F. Roussel, Taosheng Chen, Daniel Savic, R. Kiplin Guy, Stephen W. White, Anang A. Shelat, and Philip M. Potter

This study presents bromodomain-selective BET inhibitors that act as antitumor agents and demonstrates that these molecules have *in vivo* activity towards neuroblastoma, with essentially no toxicity

MOLECULAR CELL BIOLOGY

3519 The Synthetic Small Molecule FL3 Combats Intestinal Tumorigenesis via Axin1-Mediated Inhibition of Wnt/ β -Catenin Signaling

Dakota N. Jackson, Kibrom M. Alula, Yaritza Delgado-Deida, Redouane Tabti, Kevin Turner, Xuan Wang, K. Venuprasad, Rhonda F. Souza, Laurent Désaubry, and Arianne L. Theiss

Targeting of PHB1 by FL3 provides a novel mechanism to combat Wnt-driven cancers, with limited intestinal toxicity.

3530 MTH1 Inhibitor TH588 Disturbs Mitotic Progression and Induces Mitosis-Dependent Accumulation of Genomic 8-oxodG

Sean G. Rudd, Helge Gad, Kumar Sanjiv, Nuno Amaral, Anna Hagenkort, Petra Groth, Cecilia E. Ström, Oliver Mortusewicz, Ulrika Warpman Berglund, and Thomas Helleday

These findings uncover a novel link between accumulation of genomic 8-oxodG and perturbed mitotic progression in cancer cells, which can be exploited therapeutically using MTH1 inhibitors.

See related commentary, p. 3459

3542 Oxygen-Enhanced Optoacoustic Tomography Reveals the Effectiveness of Targeting Heme and Oxidative Phosphorylation at Normalizing Tumor Vascular Oxygenation

Poorva Ghosh, Yihang Guo, Adnin Ashrafi, Jingyu Chen, Sanchareeka Dey, Shigen Zhong, Jie Liu, James Campbell, Purna Chaitanya Konduri, Jeni Gerberich, Massoud Garrossian, Ralph P. Mason, Li Zhang, and Li Liu

Heme-targeting agents HSP2 and CycT effectively normalize tumor vasculature and alleviate tumor hypoxia, raising the possibility of their combination with chemo-, radio-, and immunotherapies to improve antitumor efficacy.

See related commentary, p. 3461

3556 Epigenetic CRISPR Screens Identify *Npm1* as a Therapeutic Vulnerability in Non-Small Cell Lung Cancer

Fei Li, Wai-Lung Ng, Troy A. Luster, Hai Hu, Vladislav O. Sviderskiy, Catriona M. Dowling, Kate E.R. Hollinshead, Paula Zouitine, Hua Zhang, Qingyuan Huang, Michela Ranieri, Wei Wang, Zhaoyuan Fang, Ting Chen, Jiehui Deng, Kai Zhao, Hon-Cheong So, Alireza Khodadadi-Jamayran, Mousheng Xu, Angeliki Karatza, Val Pyon, Shuai Li, Yuanwang Pan, Kristen Labbe, Christina Almonte, John T. Poirier, George Miller, Richard Possemato, Jun Qi, and Kwok-Kin Wong

Epigenome-wide CRISPR knockout screens identify *NPM1* as a novel metabolic vulnerability and demonstrate that targeting *NPM1* is a new therapeutic opportunity for patients with NSCLC.

3588 Cancer-Associated Point Mutations in the *DLC1* Tumor Suppressor and Other Rho-GAPs Occur Frequently and Are Associated with Decreased Function



Dunrui Wang, Xiaolan Qian, Beatriz Sanchez-Solana, Brajendra K. Tripathi, Marian E. Durkin, and Douglas R. Lowy

These findings indicate that point mutation of Rho-GAP genes is unexpectedly frequent in several cancer types, with *DLC1* mutants exhibiting reduced function by various mechanisms.

3580 FIP200 Suppresses Immune Checkpoint Therapy Responses in Breast Cancers by Limiting AZI2/TBK1/IRF Signaling Independent of its Canonical Autophagy Function

Takako Okamoto, Syn Kok Yeo, Mingang Hao, Mary Rose Copley, Michael A. Haas, Song Chen, and Jun-Lin Guan

These findings show that deletion of FIP200 enhances immune checkpoint inhibitor efficacy in nonresponsive breast cancer.

3593 Calibration of Pathogenicity Due to Variant-Induced Leaky Splicing Defects by Using *BRCA2* Exon 3 as a Model System

Hélène Tubeuf, Sandrine M. Caputo, Teresa Sullivan, Julie Rondeaux, Sophie Krieger, Virginie Caux-Moncoutier, Julie Hauchard, Gaia Castelain, Alice Fiévet, Laëticia Meulemans, Françoise Révillion, Mélanie Léoné, Nadia Boutry-Kryza, Capucine Delnatte, Marine Guillaud-Bataille, Linda Cleveland, Susan Reid, Eileen Southon, Omar Soukariéh, Aurélie Drouet, Daniela Di Giacomo, Myriam Vezain, Françoise Bonnet-Dorion, Violaine Bourdon, Hélène Larbre, Danièle Muller, Pascal Pujol, Fátima Vaz, Séverine Audebert-Bellanger, Chrystelle Colas, Laurence Venat-Bouvet, Angela R. Solano, Dominique Stoppa-Lyonnet, Claude Houdayer, Thierry Frebourg, Pascaline Gaildrat, Shyam K. Sharan, and Alexandra Martins

These findings demonstrate that *BRCA2* tumor suppressor function tolerates substantial reduction in full-length transcripts, helping to determine the pathogenicity of *BRCA2* leaky splicing variants, some of which may not increase cancer risk.

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TUMOR BIOLOGY AND IMMUNOLOGY

- 3606 Cellular Senescence Promotes Skin Carcinogenesis through p38MAPK and p44/42MAPK Signaling**
Fatouma Alimirah, Tanya Pulido, Alexis Valdovinos, Sena Alptekin, Emily Chang, Elijah Jones, Diego A. Diaz, Jose Flores, Michael C. Velarde, Marco Demaria, Albert R. Davalos, Christopher D. Wiley, Chandani Limbad, Pierre-Yves Desprez, and Judith Campisi
These findings identify chemotherapy-induced senescence as a culprit behind tumor promotion, suggesting that elimination of senescent cells after chemotherapy may reduce occurrence of second cancers decades later.
- 3620 Rb and p53 Execute Distinct Roles in the Development of Pancreatic Neuroendocrine Tumors**
Yuki Yamauchi, Yuzo Kodama, Masahiro Shiokawa, Nobuyuki Kakiuchi, Saiko Marui, Takeshi Kuwada, Yuko Sogabe, Teruko Tomono, Atsushi Mima, Toshihiro Morita, Tomoaki Matsumori, Tatsuki Ueda, Motoyuki Tsuda, Yoshihiro Nishikawa, Katsutoshi Kuriyama, Yojiro Sakuma, Yuji Ota, Takahisa Maruno, Norimitsu Uza, Atsuhiko Masuda, Hisato Tatsuoka, Daisuke Yabe, Sachiko Minamiguchi, Toshihiko Masui, Nobuya Inagaki, Shinji Uemoto, Tsutomu Chiba, and Hiroshi Seno
Pancreas-specific manipulation of *Rb* and *p53* genes induced malignant transformation of islet cells, reproducing stepwise progression from microadenomas to indolent (grade 1) and subsequent aggressive PanNETs (grade 2-3).
- 3631 A Pygo2-Histone Interaction Is Critical for Cancer Cell Dedifferentiation and Progression in Malignant Breast Cancer**
Meera Saxena, Ravi K.R. Kalathur, Natalia Rubinstein, Andrea Vettiger, Nami Sugiyama, Melanie Neutzner, Mairene Coto-Llerena, Venkatesh Kancharla, Caner Ercan, Salvatore Piscuoglio, Jonas Fischer, Ernesta Fagiani, Claudio Cantù, Konrad Basler, and Gerhard Christofori
Pygo2 represents a potential therapeutic target in metastatic breast cancer, as its histone-binding capability promotes β -catenin-mediated Wnt signaling and transcriptional control in breast cancer cell dedifferentiation, EMT, and metastasis.
- 3649 HDAC6 Plays a Noncanonical Role in the Regulation of Antitumor Immune Responses, Dissemination, and Invasiveness of Breast Cancer**
Debarati Banik, Satish Noonpalle, Melissa Hadley, Erica Palmer, Maria Gracia-Hernandez, Christian Zevallos-Delgado, Namratta Manhas, Hayk Simonyan, Colin N. Young, Anastas Popratiloff, Katherine B. Chiappinelli, Rohan Fernandes, Eduardo M. Sotomayor, and Alejandro Villagra
Ultrasensitive HDAC6 inhibitors can reduce tumor growth and invasiveness of breast cancer by noncanonical mechanisms unrelated to the previously cytotoxic properties attributed to HDAC inhibitors.

- 3663 Palmitoylated Proteins on AML-Derived Extracellular Vesicles Promote Myeloid-Derived Suppressor Cell Differentiation via TLR2/Akt/mTOR Signaling**
Sehmus Tohumeken, Rebecca Baur, Martin Böttcher, Andrej Stoll, Romy Loschinski, Konstantinos Panagiotidis, Martina Braun, Domenica Saul, Simon Völkl, Andreas S. Baur, Heiko Bruns, Andreas Mackensen, Regina Jitschin, and Dimitrios Mougiakakos
These findings indicate that targeting protein palmitoylation in AML could interfere with the leukemogenic potential and block MDSC accumulation to improve immunity.
- 3677 Monocyte-Derived Leukemia-Associated Macrophages Facilitate Extramedullary Distribution of T-cell Acute Lymphoblastic Leukemia Cells**
AC
Feifei Yang, Wenli Feng, Hao Wang, Lina Wang, Xiaoli Liu, Rong Wang, Chong Chen, Xiao Yang, Dongyue Zhang, Qian Ren, and Guoguang Zheng
This study links monocyte-derived leukemia-associated macrophages with noninfectious inflammation and extramedullary distribution of leukemia cells during leukemia progression, providing new insight into macrophage-based immunotherapy in leukemia.
- 3692 Deletion of Glutathione S-Transferase Omega 1 Activates Type I Interferon Genes and Downregulates Tissue Factor**
AC
Yibin Xu, Armand Bankhead III, Xiaoli Tian, Jianming Tang, Mats Ljungman, and Nouri Neamati
These findings validate GSTO1 as a therapeutic target in cancer and implicate GSTO1 in the modulation of tumor growth, immune responses, and expression of F3.

TRANSLATIONAL SCIENCE

- 3706 Suppression of ABCE1-Mediated mRNA Translation Limits N-MYC-Driven Cancer Progression**
Jixuan Gao, MoonSun Jung, Chelsea Mayoh, Pooja Venkat, Katherine M. Hannan, Jamie I. Fletcher, Alvin Kamili, Andrew J. Gifford, Eric P. Kusnadi, Richard B. Pearson, Ross D. Hannan, Michelle Haber, Murray D. Norris, Klaartje Somers, and Michelle J. Henderson
These findings demonstrate that N-MYC-driven cancers are reliant on elevated rates of protein synthesis driven by heightened expression of ABCE1, a vulnerability that can be exploited through suppression of ABCE1.
- 3719 KRAS^{G61H} Preferentially Signals through MAPK in a RAF Dimer-Dependent Manner in Non-Small Cell Lung Cancer**
AC
Zhi-Wei Zhou, Chiara Ambrogio, Asim K. Bera, Qing Li, Xing-Xiao Li, Lianbo Li, Jieun Son, Sudershan Gondi, Jiaqi Li, Emily Campbell, Hua Jin, Jeffrey J. Okoro, Cheng-Xiong Xu, Pasi A. Janne, and Kenneth D. Westover
These findings show that oncogenic KRAS^{G61H} forms a cooperative RAS-RAF ternary complex, which renders RAS-driven tumors vulnerable to MEKi and RAFi, thus establishing a framework for evaluating RAS biomarker-driven targeted therapies.

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3732 **A Rare *TP53* Mutation Predominant in Ashkenazi Jews Confers Risk of Multiple Cancers**

Jacquelyn Powers, Emilia M. Pinto, Thibaut Barnoud, Jessica C. Leung, Tetyana Martynyuk, Andrew V. Kossenkov, Aaron H. Philips, Heena Desai, Ryan Hausler, Gregory Kelly, Anh N. Le, Marilyn M. Li, Suzanne P. MacFarland, Louise C. Pyle, Kristin Zelley, Katherine L. Nathanson, Susan M. Domchek, Thomas P. Slavin, Jeffrey N. Weitzel, Jill E. Stopfer, Judy E. Garber, Vijai Joseph, Kenneth Offit, Jill S. Dolinsky, Stephanie Gutierrez, Kelly McGoldrick, Fergus J. Couch, Brooke Levin, Morris C. Edelman, Carolyn Fein Levy, Sheri L. Spunt, Richard W. Kriwacki, Gerard P. Zambetti, Raul C. Ribeiro, Maureen E. Murphy, and Kara N. Maxwell
TP53 c.1000C>G;p.G334R is a pathogenic, Ashkenazi Jewish-predominant mutation associated with a familial multiple cancer syndrome in which carriers should undergo screening and preventive measures to reduce cancer risk.

CONVERGENCE AND TECHNOLOGIES

3745 **Nonlinear Optics with Near-Infrared Excitation Enable Real-Time Quantitative Diagnosis of Human Cervical Cancers**

AC

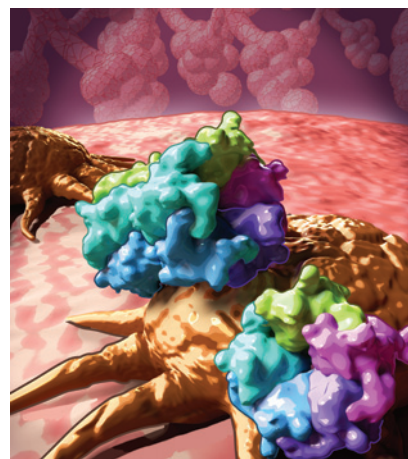
Takahiro Matsui, Ryo Tamoto, Akio Iwasa, Masafumi Mimura, Seiji Taniguchi, Tetsuo Hasegawa, Takao Sudo, Hiroki Mizuno, Junichi Kikuta, Ichiro Onoyama, Kaoru Okugawa, Mayu Shiomi, Shinya Matsuzaki, Eiichi Morii, Tadashi Kimura, Kiyoko Kato, Yasujiro Kiyota, and Masaru Ishii
This study proposes a novel method for diagnosing cancer using nonlinear optics, which enables visualization of histological features of living tissues without the need for any biopsy or staining dye.

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ABOUT THE COVER

Despite advancements in treatment options, the overall cure and survival rates for non-small cell lung cancers (NSCLC) remain low. Using epigenome-wide CRISPR knockout screens, the histone chaperone nucleophosmin 1 (NPM1) was identified as a potential therapeutic target. Furthermore, genetic ablation of NPM1 rewired the balance of metabolism in cancer cells from predominant aerobic glycolysis to oxidative phosphorylation and reduced the population of tumor-propagating cells. The cover image shows that pentameric NPM1 is a therapeutic target for tumor-propagating cells in NSCLC. The pentameric protein is depicted in five different colors. Alveoli in the background show the context of NSCLC. For details, see article by Li and colleagues on page 3556.



POPULATION AND PREVENTION SCIENCE

3755 **A Novel Locus Predicts Spermatogenic Recovery among Childhood Cancer Survivors Exposed to Alkylating Agents**

Yadav Sapkota, Carmen L. Wilson, Asifa K. Zaidi, Wonjong Moon, Klementina Fon Tacer, Lu Lu, Qi Liu, Jessica Baedke, Rikeenkumar Dhaduk, Zhaoming Wang, Wassim Chemaitilly, Matthew J. Krasin, Fred B. Berry, Jinghui Zhang, Melissa M. Hudson, Leslie L. Robison, Daniel M. Green, and Yutaka Yasui

The identified genetic markers harbor potential clinical utility in characterizing high-risk survivors and guiding intervention strategies including pretreatment patient counseling and use of fertility preservation services.

3765 **Physical Activity Does Not Lower the Risk of Lung Cancer**

Sebastian-Edgar Baumeister, Michael F. Leitzmann, Martin Bahls, Christa Meisinger, Christopher I. Amos, Rayjean J. Hung, Cancer in Lung of the International Lung Cancer Consortium, Lung Cancer Cohort Consortium, Alexander Teumer, and Hansjörg Baurecht
A new genetic study provides little evidence that recommending physical activity would help prevent lung cancer.

Cancer Research

The Journal of Cancer Research (1916–1930) | The American Journal of Cancer (1931–1940)

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