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See related article by O'Reilly and colleagues, *Cancer Res* 2006;66:1500–8

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6090 Combinatorial CRISPR/Cas9 Screening Reveals Epistatic Networks of Interacting Tumor Suppressor Genes and Therapeutic Targets in Human Breast Cancer
Xiaoyu Zhao, Jinyu Li, Zhimin Liu, and Scott Powers
This study provides a roadmap for moving beyond discovery and development of therapeutic strategies based on single driver gene analysis to discovery based on interactions between multiple driver genes.

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6106 Cancer Mutational Processes Vary in Their Association with Replication Timing and Chromatin Accessibility
Adar Yaacov, Oriya Vardi, Britny Blumenfeld, Avraham Greenberg, Dashiell J. Massey, Amnon Koren, Sheera Adar, Itamar Simon, and Shai Rosenberg
Many mutational processes associate with early or late replication timing regions independently of chromatin accessibility, enabling development of a focused identification approach to improve mutational signature detection.

6117 Activation of *Notch* and *Myc* Signaling via B-cell-Restricted Depletion of *Dnmt3a* Generates a Consistent Murine Model of Chronic Lymphocytic Leukemia
Anat Biran, Shanye Yin, Helene Kretzmer, Elisa ten Hacken, Salma Parvin, Fabienne Lucas, Mohamed Uduman, Catherine Gutierrez, Nathan Dangle, Leah Billington, Fara Faye Regis, Laura Z. Rassenti, Arman Mohammad, Gabriela Brunsting Hoffmann, Kristen Stevenson, Mei Zheng, Elizabeth Witten, Stacey M. Fernandes, Eugen Tausch, Clare Sun, Stephan Stilgenbauer, Jennifer R. Brown, Thomas J. Kipps, John C. Aster, Andreas Gnirke, Donna S. Neuberg, Anthony Letai, Lili Wang, Ruben D. Carrasco, Alexander Meissner, and Catherine J. Wu

Loss of *DNMT3A* expression is a driving event in CLL and is associated with aggressive disease, activation of *Notch* and *Myc* signaling, and enhanced sensitivity to *Notch* inhibition.

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MOLECULAR CELL BIOLOGY

- 6131** **SOX10 Regulates Melanoma Immunogenicity through an IRF4-IRF1 Axis**
Satoru Yokoyama, Atsushi Takahashi, Ryota Kikuchi, Soshi Nishibu, Jennifer A. Lo, Miroslav Hejna, Wooyoung M. Moon, Shinichiro Kato, Yue Zhou, F. Stephen Hodi, Jun S. Song, Hiroaki Sakurai, David E. Fisher, and Yoshihiro Hayakawa
This study identifies a novel SOX10/IRF4 pathway that regulates noncanonical induction of IRF1 independent of the JAK-STAT pathway and can be targeted to improve the efficacy of anti-PD-1 therapy in melanoma.

- 6142** ***Circ0008399* Interaction with WTAP Promotes Assembly and Activity of the m⁶A Methyltransferase Complex and Promotes Cisplatin Resistance in Bladder Cancer**
Wenjie Wei, Jiayin Sun, Hui Zhang, Xingyuan Xiao, Chao Huang, Liang Wang, He Zhong, Yangkai Jiang, Xiaoping Zhang, and Guosong Jiang
A newly characterized circRNA *circ0008399* binds WTAP to modulate expression of target RNA through m⁶A modification and reduce cisplatin sensitivity in bladder cancer, implicating the potential therapeutic value of targeting this axis.

- 6157** **ANGPTL4-Mediated Promotion of Glycolysis Facilitates the Colonization of *Fusobacterium nucleatum* in Colorectal Cancer**
Xin Zheng, Rui Liu, Chenchen Zhou, Haopeng Yu, Wanyi Luo, Jianhui Zhu, Jiaxin Liu, Zhe Zhang, Na Xie, Xian Peng, Xin Xu, Lei Cheng, Quan Yuan, Canhua Huang, and Xuedong Zhou
F. nucleatum colonization in colorectal cancer is regulated by ANGPTL4-mediated glycolysis, suggesting that this axis could be targeted for combined repression of *F. nucleatum* and cancer progression.

TUMOR BIOLOGY AND IMMUNOLOGY

- 6171** **A BRCA1 Coiled-Coil Domain Variant Disrupting PALB2 Interaction Promotes the Development of Mammary Tumors and Confers a Targetable Defect in Homologous Recombination Repair**
Emilia M. Pulver, Chirantani Mukherjee, Gerarda van de Kamp, Stefan J. Roobol, Magdalena B. Rother, Hanneke van der Gulden, Roebi de Bruijn, Maria Valeria Lattanzio, Eline van der Burg, Anne Paulien Drenth, Nicole S. Verkaik, Kerstin Hahn, Sjoerd Klarenbeek, Renske de Korte-Grimmerink, Marieke van de Ven, Colin E.J. Pritchard, Ivo J. Huijbers, Bing Xia, Dik C. van Gent, Jeroen Essers, Haico van Attikum, Arnab Ray Chaudhuri, Peter Bouwman, and Jos Jonkers
These findings reveal the importance of a patient-derived BRCA1 coiled-coil domain sequence variant in embryonic development, mammary tumor suppression, and therapy response.

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- 6183** **Neoadjuvant *In Situ* Immunomodulation Enhances Systemic Antitumor Immunity against Highly Metastatic Tumors**
Takaaki Oba, Ryutarō Kajihara, Toshihiro Yokoi, Elizabeth A. Repasky, and Fumito Ito
Neoadjuvant induction and activation of cDC1s in primary tumors enhances systemic antitumor immunity, suppresses metastatic progression, improves survival, and synergizes with anti-PD-L1 therapy.

- 6196** **Heterogeneity of Circulating Tumor Cell-Associated Genomic Gains in Breast Cancer and Its Association with the Host Immune Response**
Nisha Kanwar, Zaldy Balde, Ranju Nair, Melanie Dawe, Shiyi Chen, Manjula Maganti, Eshetu G. Atenafu, Sabrina Manolescu, Carrie Wei, Amanda Mao, Fred Fu, Dan Wang, Alison Cheung, Yulia Yerofeyeva, Rachel Peters, Kela Liu, Christine Desmedt, Christos Sotiriou, Borbala Szekely, Janina Kulka, Trevor D. McKee, Naoto Hirano, John M.S. Bartlett, Martin J. Yaffe, Philippe L. Bedard, David McCready, and Susan J. Done
As breast cancers progress, they become more heterogeneous for multiple regions amplified in circulating tumor cells, and intratumoral spatial heterogeneity is associated with the immune landscape.

TRANSLATIONAL SCIENCE

- 6207** **HER3 Is an Actionable Target in Advanced Prostate Cancer**
Veronica Gil, Susana Miranda, Ruth Riisnaes, Bora Gurel, Mariantonietta D'Ambrosio, Alessandro Vasciaveo, Mateus Crespo, Ana Ferreira, Daniela Brina, Martina Troiani, Adam Sharp, Beshara Sheehan, Rossitza Christova, George Seed, Ines Figueiredo, Maryou Lambros, David Dolling, Jan Rekowski, Abdullah Alajati, Matthew Clarke, Rita Pereira, Penny Flohr, Gemma Fowler, Gunther Boysen, Semini Sumanasuriya, Diletta Bianchini, Pasquale Rescigno, Caterina Aversa, Nina Tunariu, Christina Guo, Alec Paschalis, Claudia Bertan, Lorenzo Buroni, Jian Ning, Suzanne Carreira, Paul Workman, Amanda Swain, Andrea Califano, Michael M. Shen, Andrea Alimonti, Antje Neeb, PCF/SU2C International Prostate Cancer Dream Team, Jonathan Welti, Wei Yuan, and Johann de Bono
HER3 is an actionable target in prostate cancer, especially with anti-HER3 immunoconjugates, and targeting HER3 warrants clinical evaluation in prospective trials.

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6219 A Combinatorial CRISPR–Cas9 Screen Identifies Iifenprodil as an Adjunct to Sorafenib for Liver Cancer Treatment

Feng Xu, Man Tong, Cindy S.W. Tong, Becky K.C. Chan, Hoi Yee Chu, Tin Lok Wong, John H.C. Fong, Maggie S.H. Cheung, Kylie Hin-Man Mak, Lakhansing Pardeshi, Yuanhua Huang, Koon Ho Wong, Gigi C.G. Choi, Stephanie Ma, and Alan S.L. Wong
Combinatorial CRISPR–Cas9 screening identifies actionable targets for HCC therapy, uncovering the potential of combining the clinically approved drugs iifenprodil and sorafenib as a new effective treatment regimen.

6233 A Dual PI3K/HDAC Inhibitor Induces Immunogenic Ferroptosis to Potentiate Cancer Immune Checkpoint Therapy

Fushun Fan, Pei Liu, Rudi Bao, Jian Chen, Minhua Zhou, Zhenxian Mo, Yaru Ma, Haiqi Liu, Yiping Zhou, Xiong Cai, Changgeng Qian, and Xinjian Liu
The dual PI3K/HDAC inhibitor BEBT-908 elicits potent anti-tumor responses, effectively inducing immunogenic ferroptosis of tumor cells and potentiating cancer immunotherapy.

6246 BRD4 Regulates Transcription Factor Δ Np63 α to Drive a Cancer Stem Cell Phenotype in Squamous Cell Carcinomas

Matthew L. Fisher, Seamus Balinth, Yon Hwangbo, Caizhi Wu, Carlos Ballon, John E. Wilkinson, Gary L. Goldberg, and Alea A. Mills
This study identifies a signaling cascade driven by BRD4 that upregulates Δ Np63 α to promote cancer stem-like properties, which has potential therapeutic implications for the treatment of squamous cell carcinomas.

6259 Transcriptional Reprogramming Differentiates Active from Inactive ESR1 Fusions in Endocrine Therapy-Refractory Metastatic Breast Cancer

Xuxu Gou, Meenakshi Anurag, Jonathan T. Lei, Beom-Jun Kim, Purba Singh, Sinem Seker, Diana Fandino, Airi Han, Saif Rehman, Jianhong Hu, Viktoriya Korchina, Harshavardhan Doddapaneni, Lacey E. Dobrolecki, Nicholas Mitsiades, Michael T. Lewis, Alana L. Welm, Shunqiang Li, Adrian V. Lee, Dan R. Robinson, Charles E. Foulds, and Matthew J. Ellis
This study identifies a gene signature diagnostic for functional ESR1 fusions that drive poor outcome in advanced breast cancer, which could also help guide precision medicine approaches in patients harboring *ESR1* mutations.

POPULATION AND PREVENTION SCIENCE

6273 Longitudinal SARS-CoV-2 mRNA Vaccine-Induced Humoral Immune Responses in Patients with Cancer

Jane C. Figueiredo, Noah M. Merin, Omid Hamid, So Yung Choi, Tucker Lemos, Wendy Cozen, Nathalie Nguyen, Laurel J. Finster, Joslyn Foley, Justin Darrah, Jun Gong, Ronald Paquette, Alain C. Mita, Robert Vescio, Inderjit Mehmi, Reva Basho, Warren G. Tourtellotte, Carissa A. Huynh, Gil Y. Melmed, Jonathan Braun, Dermot P.B. McGovern, Emebet Mengesha, Greg Botwin, John C. Probstko, Edwin C. Frias, James L. Stewart, Sandy Joung, Jennifer Van Eyk, Joseph E. Ebinger, Susan Cheng, Kimia Sobhani, Karen L. Reckamp, and Akil Merchant
Long-term studies of immunogenicity of SARS-CoV-2 vaccines in patients with cancer are needed to inform evidence-based guidelines for booster vaccinations and to tailor sequence and timing of vaccinations to elicit improved humoral responses.

ABOUT THE COVER

Multiple *ESR1* gene fusions have been recently identified in estrogen receptor alpha-positive (ER α^+) metastatic breast cancer (depicted by the Circos plot). Active ER α fusion proteins enter the nucleus (depicted by the immunofluorescence) and drive estrogen-independent transcription of estrogen response and epithelial-to-mesenchymal transition genes (depicted by the heatmap), which form a diagnostic 24-gene signature (depicted by the ROC curve). This signature accurately diagnosed the presence of active *ESR1* fusions and mutations expressed in ER α^+ patient-derived xenografts and metastatic breast cancer patients. For details, see the article by Gou and colleagues on page 6259.

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