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### Science in Society

**From the Community to the Bench and Back Again: The Value of Patient and Community Engagement in Cancer Research** ..... 2135  
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**Tissue-Agnostic Drug Development: A New Path to Drug Approval** ..... 2139  
K.Z. Thein, S.J. Lemery, and S. Kummar

**REVIEW** Targeting *EGFR* Exon 20 Insertions in Non-Small Cell Lung Cancer: Recent Advances and Clinical Updates ..... 2145  
C.B. Meador, L.V. Sequist, and Z. Piotrowska

**RESEARCH BRIEF** Reducing Skin Toxicities from *EGFR* Inhibitors with Topical *BRAF* Inhibitor Therapy ..... 2158  
M.E. Lacouture, Z.A. Wainberg, A.B. Patel, M.J. Anadkat, S.M. Stemmer, E. Shacham-Shmueli, E. Medina, G. Zelinger, N. Shelach, and A. Ribas

**Précis:** In a phase I trial, topical application of a gel formulation of a *BRAF* inhibitor was safe and provided early evidence of improvement of acneiform rash induced by *EGFR* inhibitor therapy.

**RESEARCH ARTICLES** Determinants of Response and Intrinsic Resistance to PD-1 Blockade in Microsatellite Instability-High Gastric Cancer ..... 2168



M. Kwon, M. An, S.J. Klempner, H. Lee, K.-M. Kim, J.K. Sa, H.J. Cho, J.Y. Hong, T. Lee, Y.W. Min, T.J. Kim, B.-H. Min, W.-Y. Park, W.K. Kang, K.-T. Kim, S.T. Kim, and J. Lee

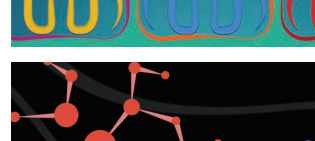
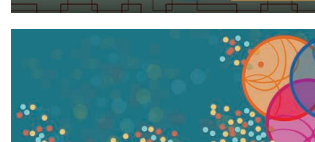
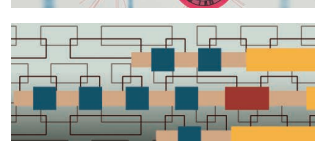
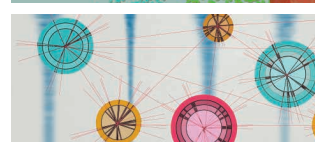
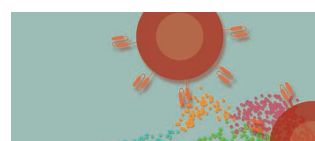
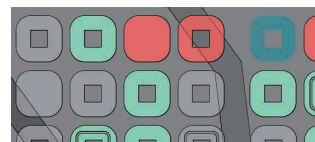
**Précis:** Prospective genomic and immunologic analysis of on-treatment tissue and peripheral blood provides insight into the heterogeneity of response to pembrolizumab monotherapy among patients with MSI-high gastric cancer.

See commentary, p. 2126

**Integrative Bulk and Single-Cell Profiling of Premanufacture T-cell Populations Reveals Factors Mediating Long-Term Persistence of CAR T-cell Therapy** ..... 2186



G.M. Chen, C. Chen, R.K. Das, P. Gao, C.-H. Chen, S. Bandyopadhyay, Y.-Y. Ding, Y. Uzun, W. Yu, Q. Zhu, R.M. Myers, S.A. Grupp, D.M. Barrett, and K. Tan





**Précis:** A bulk and single-cell atlas of premanufacture T-cells was generated from 71 patients on trial treated with anti-CD19 CAR T-cell therapy, and integrative analysis identified key molecular factors associated with clinical CAR T-cell persistence.

**ZFTA-RELA Dictates Oncogenic Transcriptional Programs to Drive Aggressive Supratentorial Ependymoma ..... 2200**

A. Arabzade, Y. Zhao, S. Varadharajan, H.-C. Chen, S. Jessa, B. Rivas, A.J. Stuckert, M. Solis, A. Kardian, D. Tlais, B.J. Golbourn, A.J. Stanton, Y.S. Chan, C. Olson, K.L. Karlin, K. Kong, R. Kupp, B. Hu, S.G. Injac, M. Ngo, P.R. Wang, L.A. De León, F. Sahm, D. Kawauchi, S.M. Pfister, C.Y. Lin, H.C. Hodges, I. Singh, T.F. Westbrook, M.M. Chintagumpala, S.M. Blaney, D.W. Parsons, K.W. Pajtler, S. Agnihotri, R.J. Gilbertson, J. Yi, N. Jabado, C.L. Kleinman, K.C. Bertrand, B. Deneen, and S.C. Mack

**Précis:** The ZFTA-RELA fusion protein engages DNA and regulates chromatin structure to direct transcriptional programs that lead to ependymoma brain tumor development.

**ZFTA Translocations Constitute Ependymoma Chromatin Remodeling and Transcription Factors ..... 2216**

R. Kupp, L. Ruff, S. Terranova, E. Nathan, S. Ballereau, R. Stark, C. Sekhar Reddy Chilamakuri, N. Hoffmann, K. Wickham-Rahrmann, M. Widdess, A. Arabzade, Y. Zhao, S. Varadharajan, T. Zheng, M. Murugesan, S.M. Pfister, D. Kawauchi, K.W. Pajtler, B. Deneen, S.C. Mack, K.E. Masih, B.E. Gryder, J. Khan, and R.J. Gilbertson

**Précis:** Cross-species multi-omic and mouse modelling studies revealed ependymoma ZFTA (also known as C11orf95) fusion oncoproteins to be aberrant transcription factors with promiscuous chromatin binding and remodelling properties.

**Cross-Species Genomics Reveals Oncogenic Dependencies in ZFTA/C11orf95 Fusion-Positive Supratentorial Ependymomas ..... 2230**

T. Zheng, D.R. Ghasemi, K. Okonechnikov, A. Korshunov, M. Sill, K.K. Maass, P. Benites Goncalves da Silva, M. Ryzhova, J. Gojo, D. Stichel, A. Arabzade, R. Kupp, J. Benzell, S. Taya, T. Adachi, R. Shiraishi, N.U. Gerber, D. Sturm, J. Ecker, P. Sievers, F. Selt, R. Chapman, C. Haberler, D. Figarella-Branger, G. Reifenberger, G. Fleischhack, S. Rutkowski, A.M. Donson, V. Ramaswamy, D. Capper, D.W. Ellison,

C.C. Herold-Mende, U. Schüller, S. Brandner, P. Hernáiz Driever, J.M. Kros, M. Snuderl, T. Milde, R.G. Grundy, M. Hoshino, S.C. Mack, R.J. Gilbertson, D.T.W. Jones, M. Kool, A. von Deimling, S.M. Pfister, F. Sahm, D. Kawauchi, and K.W. Pajtler

**Précis:** Molecular refinement and cross-species genomics of supratentorial ependymoma revealed a central role for the fusion partner ZFTA associated with potential therapeutic vulnerabilities.

**IFN $\gamma$  Is Critical for CAR T Cell-Mediated Myeloid Activation and Induction of Endogenous Immunity ..... 2248**

 D. Alizadeh, R.A. Wong, S. Gholamin, M. Maker, M. Aftabizadeh, X. Yang, J.R. Pecoraro, J.D. Jeppson, D. Wang, B. Aguilar, R. Starr, C.B. Larmonier, N. Larmonier, M.-H. Chen, X. Wu, A. Ribas, B. Badie, S.J. Forman, and C.E. Brown

**Précis:** In addition to direct antigen-dependent tumor targeting, CAR T-cell production of IFN $\gamma$  can activate host myeloid and T cells to induce antitumor immunity and promote effective CAR T-cell therapy for solid tumors.

**Discovery of Candidate DNA Methylation Cancer Driver Genes ..... 2266**

 H. Pan, L. Renaud, R. Chaligne, J. Bloehdorn, E. Tausch, D. Mertens, A.M. Fink, K. Fischer, C. Zhang, D. Betel, A. Gnirke, M. Imielinski, J. Moreaux, M. Hallek, A. Meissner, S. Stilgenbauer, C.J. Wu, O. Elemento, and D.A. Landau

**Précis:** MethSig, a novel statistical framework for the analysis of DNA methylation changes in cancer, identifies candidate DNA methylation cancer driver events with high accuracy across cancer types and after relapse, as well as drivers predictive of clinical outcome.

**Selective Modulation of a Pan-Essential Protein as a Therapeutic Strategy in Cancer ..... 2282**

C.F. Malone, N.V. Dharia, G. Kugener, A.B. Forman, M.V. Rothberg, M. Abdusamad, A. Gonzalez, M. Kuljanin, A.L. Robichaud, A. Saur Conway, J.M. Dempster, B.R. Paoletta, N. Dumont, V. Hovestadt, J.D. Mancias, S.T. Younger, D.E. Root, T.R. Golub, F. Vazquez, and K. Stegmaier

**Précis:** Functional genomic screens uncover nuclear export factor NXT1 as a selectively lethal dependency in neuroblastoma due to context-specific loss of its binding partner, the essential protein NXF1.

*See commentary, p. 2129*

### Transcriptional Silencing of *ALDH2* Confers a Dependency on Fanconi Anemia Proteins in Acute Myeloid Leukemia .....2300



Z. Yang, X.S. Wu, Y. Wei, S.A. Polyanskaya, S.V. Iyer, M. Jung, F.P. Lach, E.R. Adelman, O. Klingbeil, J.P. Milazzo, M. Kramer, O.E. Demerdash, K. Chang, S. Goodwin, E. Hodges, W.R. McCombie, M.E. Figueroa, A. Smogorzewska, and C.R. Vakoc

**Précis:** Blockade of the ubiquitination reaction catalyzed by Fanconi anemia proteins selectively suppresses leukemia cells by exploiting an epigenetics-based synthetic lethal interaction with the aldehyde detoxifying enzyme *ALDH2*.

### NKX3.1 Localization to Mitochondria Suppresses Prostate Cancer Initiation .....2316

A. Papachristodoulou, A. Rodriguez-Calero, S. Panja, E. Margolskee, R.K. Virk, T.A. Milner, L. Pina Martina, J.Y. Kim, M. Di Bernardo, A.B. Williams, E.A. Maliza, J.M. Caputo, C. Haas, V. Wang, G.J. De Castro, S. Wenske, H. Hibshoosh, J.M. McKiernan, M.M. Shen, M.A. Rubin, A. Mitrofanova, A. Dutta, and C. Abate-Shen

**Précis:** Oxidative stress promotes NKX3.1 import to mitochondria where it restores oxidative phosphorylation and prevents cancer initiation, thus uncovering a nonnuclear function for a homeoprotein in suppression of cancer.

See commentary, p. 2132

### RB/E2F1 as a Master Regulator of Cancer Cell Metabolism in Advanced Disease .....2334



A.C. Mandigo, W. Yuan, K. Xu, P. Gallagher, A. Pang, Y.F. Guan, A.A. Shafi, C. Thangavel, B. Sheehan, D. Bogdan, A. Paschalis, J.J. McCann, T.S. Laufer, N. Gordon, I.A. Vasilevskaya, E. Dylgjeri, S.N. Chand, M.J. Schiewer, J. Domingo-Domenech, R.B. Den, J. Holst, P.A. McCue, J.S. de Bono, C. McNair, and K.E. Knudsen

**Précis:** Analysis of RB-deficient cancer revealed an E2F1-dependent reprogramming of cancer metabolism and increased reliance on glutathione synthesis, nominating a new avenue to target late-stage, RB-deficient cancers.



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**ON THE COVER** Focal increases in cytosine methylation at gene promoters are widespread in human cancers and thought to contribute to silencing of tumor suppressor genes, but tools are lacking to distinguish methylation events that are oncogenic drivers from those that are merely passengers. Pan and colleagues developed MethSig, a statistical inference framework that accounts for variations in the stochastic hypermethylation rate across the genome and between patients, analogous to approaches used to identify driver mutations. Application of MethSig to bisulfite sequencing data or DNA methylation array data identified specific promoter hypermethylation events as potential drivers among a large number of candidate methylation changes, several of which were confirmed to enhance cancer cell fitness, and identified methylation events associated with poor clinical outcome and relapse. Cover artwork by SciStories. For more information, see the article by Pan and colleagues on page 2266.

doi: 10.1158/2159-8290.CD-11-9-CVR

