

**IN THIS ISSUE** Highlighted research articles.....1949

**NEWS IN BRIEF** Important news stories affecting the community.....1952

**RESEARCH WATCH** Selected highlights of recent articles of exceptional significance from the cancer literature.....1956

**ONLINE** For more News and Research Watch, visit *Cancer Discovery* online at <http://cancerdiscovery.aacrjournals.org/> CDNews.

**VIEWS In the Spotlight**  
**Express Delivery of Next-Generation CAR T Cells with Preserved Naive and Stemness Phenotypes for the Treatment of Aggressive Lymphomas.....1961**

M. Wang

*See article, p. 1982*

**FGFR Inhibition: Understanding and Overcoming Resistance...1964**

A. Tripathi, D. Li, and S.K. Pal

*See article, p. 1998*

*See article, p. 2012*

**So Grateful for My X: Sex Chromosomes Drive Differences in Glioblastoma Immunity.....1966**

E. Alspach

*See article, p. 2090*

**In Focus**  
**Challenges and Opportunities in Building a Global Representative Single-Cell and Spatial Atlas in Cancer.....1969**

J.T. Plummer and S.H.L. George

### Perspective

**A Wrinkle in TIME: How Changes in the Aging ECM Drive the Remodeling of the Tumor Immune Microenvironment....1973**

E.I. Harper and A.T. Weeraratna

**RESEARCH ARTICLES** **A Novel Autologous CAR-T Therapy, YTB323, with Preserved T-cell Stemness Shows Enhanced CAR T-cell Efficacy in Preclinical and Early Clinical Development....1982**

M.J. Dickinson, P. Barba, U. Jäger, N.N. Shah, D. Blaise, J. Briones, L. Shune, N. Boissel, A. Bondanza, L. Mariconti, A.-L. Marchal, D.S. Quinn, J. Yang, A. Price, A. Sohoni, L.M. Treanor, E.J. Orlando, J. Mataraza, J. Davis, D. Lu, X. Zhu, B. Engels, L. Moutouh-de Parseval, J.L. Brogdon, M. Moschetta, and I.W. Flinn

**Précis:** YTB323, a CD19-directed chimeric antigen receptor (CAR) T-cell therapy, retains T-cell stemness after a manufacturing process time of less than 2 days and demonstrates clinical antitumor activity at significantly lower doses than traditionally manufactured CAR T cells.

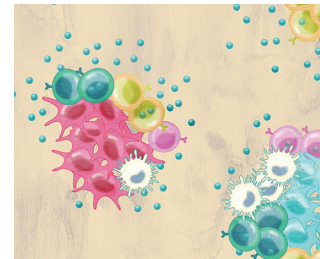
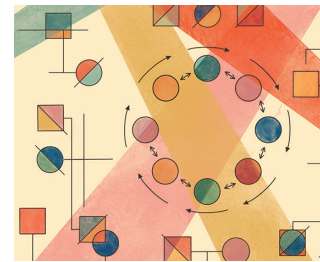
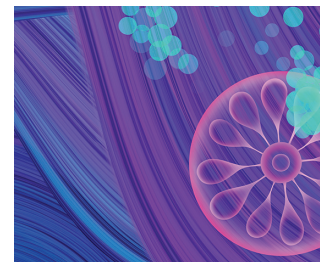
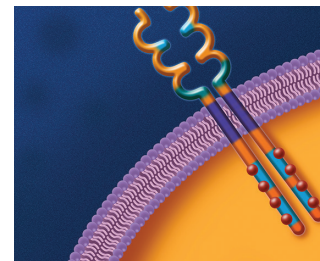
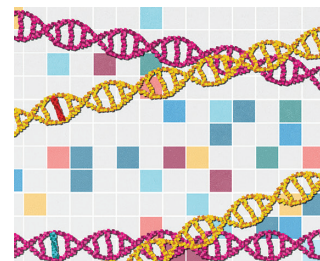
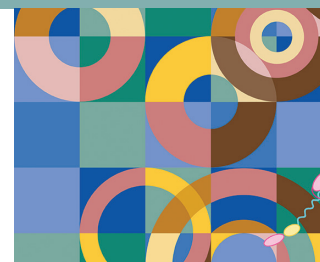
*See commentary, p. 1961*

**Resistance to Selective FGFR Inhibitors in FGFR-Driven Urothelial Cancer.....1998**

F. Facchinetti, A. Hollebecque, F. Braye, D. Vasseur, Y. Pradat, R. Bahleda, C. Pobel, L. Bigot, O. Déas, J.D. Florez Arango, G. Guaitoli, H. Mizuta, D. Combarel, L. Tselikas, S. Michiels, S.I. Nikolaev, J.-Y. Scoazec, S. Ponce-Aix, B. Besse, K.A. Olaussen, Y. Loriot, and L. Friboulet

**Précis:** In patients with FGFR-driven urothelial cancer, resistance to selective FGFR inhibitors is largely explained by the emergence of FGFR kinase domain mutations and alterations in the PI3K-mTOR pathway.

*See commentary, p. 1964*





**RLY-4008, the First Highly Selective  
FGFR2 Inhibitor with Activity across  
FGFR2 Alterations and Resistance  
Mutations** .....2012

V. Subbiah, V. Sahai, D. Maglic, K. Bruderek,  
B.B. Touré, S. Zhao, R. Valverde, P.J. O'Hearn,  
D.T. Moustakas, H. Schönherr, N. Gerami-Moayed,  
A.M. Taylor, B.M. Hudson, D.J. Houde, D. Pal,  
L. Foster, H. Gunaydin, P. Ayaz, D.A. Sharon,  
L. Goyal, A.M. Schram, S. Kamath, C.A. Sherwin,  
O. Schmidt-Kittler, K.Y. Jen, F. Ricard, B.B. Wolf,  
D.E. Shaw, D.A. Bergstrom, J. Watters, and  
J.B. Casaleto

**Précis:** Unlike pan-FGFR inhibitors, RLY-4008 was designed to be selective for FGFR2 and induces clinical responses in *FGFR2*-altered solid tumors without clinically significant FGFR1-mediated hyperphosphatemia and FGFR4-mediated diarrhea.

*See commentary, p. 1964*

**A Novel Type of Monocytic Leukemia  
Stem Cell Revealed by the Clinical Use  
of Venetoclax-Based Therapy** .....2032

S. Pei, I.T. Shelton, A.E. Gillen, B.M. Stevens,  
M. Gasparetto, Y. Wang, L. Liu, J. Liu, T.M. Brunetti,  
K. Engel, S. Staggs, W. Showers, A.I. Sheth,  
M.L. Amaya, M. Minhajuddin, A. Winters, S.B. Patel,  
H. Tolison, A.E. Krug, T.N. Young, J. Schowinsky,  
C.M. McMahon, C.A. Smith, D.A. Pollyea,  
and C.T. Jordan

**Précis:** Analyses of leukemia stem cells (LSC) in human acute myeloid leukemia (AML) revealed a type of monocytic LSC, distinct from primitive LSCs, that is responsible for the relapse/refractory response of some patients with AML treated with the BCL2 inhibitor venetoclax.

**Dynamic Glycoprotein Hyposialylation  
Promotes Chemotherapy Evasion  
and Metastatic Seeding of Quiescent  
Circulating Tumor Cell Clusters in  
Breast Cancer** .....2050

N.K. Dashzeveg, Y. Jia, Y. Zhang, L. Gerratana,  
P. Patel, A. Shajahan, T. Dandar, E.K. Ramos,  
H.F. Almubarak, V. Adorno-Cruz, R. Taftaf,  
E.J. Schuster, D. Scholten, M.T. Sokolowski,  
C. Reduzzi, L. El-Shennawy, A.D. Hoffmann,  
M. Manai, Q. Zhang, P.D'Amico, P. Azadi, K.J. Colley,  
L.C. Plataniias, A.N. Shah, W.J. Gradishar,  
M. Cristofanilli, W.A. Muller, B.A. Cobb, and H. Liu

**Précis:** In breast cancer, chemotherapy evasion is coupled to loss of glycosylation (sialylation), cellular quiescence, cluster formation of circulating tumor cells, and metastasis, with anti-PODXL-targeting approaches blocking these effects.

**FH Variant Pathogenicity Promotes  
Purine Salvage Pathway Dependence  
in Kidney Cancer** .....2072

B.R. Wilde, N. Chakraborty, N. Matulionis,  
S. Hernandez, D. Ueno, M.E. Gee, E.D. Esplin,  
K. Ouyang, K. Nykamp, B. Shuch, and H.R. Christofk

**Précis:** An investigation into the activity and metabolic consequences of patient fumarate hydratase (FH) variants showed that FH deficiency and fumarate accumulation render kidney cancer cells reliant on the purine salvage pathway for tumor growth.

**Sex-Biased T-cell Exhaustion Drives  
Differential Immune Responses in  
Glioblastoma** .....2090

J. Lee, M. Nicosia, E.S. Hong, D.J. Silver, C. Li,  
D. Bayik, D.C. Watson, A. Lauko, K.E. Kay,  
S.Z. Wang, S. Johnson, M. McGraw, M.M. Grabowski,  
D.D. Kish, A.B. Desai, W.A. Goodman, S.J. Cameron,  
H. Okada, A. Valujskikh, R.L. Fairchild,  
M.S. Ahluwalia, and J.D. Lathia

**Précis:** Sex-biased T-cell exhaustion in glioblastoma is, in part, regulated by T cell-intrinsic factors, such as the X chromosome inactivation escape gene *Kdm6a*, which highlights the potential for a precision therapy approach based on patient biologic sex.

*See commentary, p. 1966*

**Corrections**

**Correction: C/EBP $\alpha$  Confers Dependence  
to Fatty Acid Anabolic Pathways and  
Vulnerability to Lipid Oxidative  
Stress-Induced Ferroptosis in  
*FLT3*-Mutant Leukemia** .....2106

**Correction: Activity and Safety of  
Mobocertinib (TAK-788) in Previously  
Treated Non-Small Cell Lung Cancer  
with *EGFR* Exon 20 Insertion  
Mutations from a Phase I/II Trial** .....2107

### ON THE COVER

Despite the efficacy of chimeric antigen receptor (CAR) T-cell therapies in patients with B-cell malignancies, relapse after initial response is common. This has been, in part, attributed to depletion of naive and stem cell memory T-cell populations as a result of prolonged *ex vivo* culturing. In this study, Dickinson and colleagues revealed both the preclinical development as well as the preliminary clinical data of YTB323, an autologous CD19-directed CAR T-cell therapy expressing the same CAR as tisagenlecleucel that can be manufactured in less than 2 days. In preclinical mouse models, enhanced *in vivo* expansion was observed with YTB323 along with antitumor activity at lower doses than traditionally manufactured CAR T cells. Moreover, in a first-in-human trial, patients with relapsed/refractory diffuse large B-cell lymphoma demonstrated retention of T-cell stemness after YTB323 treatment, promising overall safety, and improved clinical activity at 25-fold lower doses than tisagenlecleucel, suggesting that further evaluation of this therapy is warranted. For more information, see the article by Dickinson and colleagues on page 1982. Artwork by Bianca Dunn.

doi: 10.1158/2159-8290.CD-13-9-CVR

