

IN THIS ISSUE Highlighted research articles 127

VIEWS In The Spotlight

Dual Targeting with CAR T Cells to Limit Antigen Escape in Multiple Myeloma130

S. Simon and S.R. Riddell

See article, p. 146

REVIEW Hedgehog Pathway Inhibitors: A New Therapeutic Class for the Treatment of Acute Myeloid Leukemia134

C. Jamieson, G. Martinelli, C. Papayannidis, and J.E. Cortes

RESEARCH BRIEFS Defining an Optimal Dual-Targeted CAR T-cell Therapy Approach Simultaneously Targeting BCMA and GPRC5D to Prevent BCMA Escape-Driven Relapse in Multiple Myeloma146

C. Fernández de Larrea, M. Staehr, A.V. Lopez, K.Y. Ng, Y. Chen, W.D. Godfrey, T.J. Purdon, V. Ponomarev, H.-G. Wendel, R.J. Brentjens, and E.L. Smith

Précis: CAR T cells targeting two multiple myeloma (MM) antigens are generated by orthogonal approaches, of which bicistronic vector shows superior activity, conferring long-term resistance against MM in a mouse xenograft model of antigen escape.

See commentary, p. 130

Gene Expression Profiling of Mediastinal Gray Zone Lymphoma and Its Relationship to Primary Mediastinal B-cell Lymphoma and Classical Hodgkin Lymphoma155

S. Pittaluga, A. Nicolae, G.W. Wright, C. Melani, M. Roschewski, S. Steinberg, D. Huang, L.M. Staudt, E.S. Jaffe, and W.H. Wilson

Précis: Transcriptomic and clinicopathological comparison of mediastinal gray zone lymphoma to related disorders documents intrinsic heterogeneity and refines features relevant to diagnosis and therapy.

RESEARCH ARTICLES BCOR Binding to MLL-AF9 Is Essential for Leukemia via Altered EYA1, SIX, and MYC Activity ...162

C.R. Schmidt, N.J. Achille, A. Kuntimaddi, A.M. Boulton, B.I. Leach, S. Zhang, N.J. Zeleznik-Le, and J.H. Bushweller

Précis: Structure-function characterization of AF9 complexes with BCOR and CBX8 identifies BCOR-Eya1-Myc axis in MLL-AF9-driven leukemogenesis

Combinatorial ETS1-Dependent Control of Oncogenic NOTCH1 Enhancers in T-cell Leukemia ...178

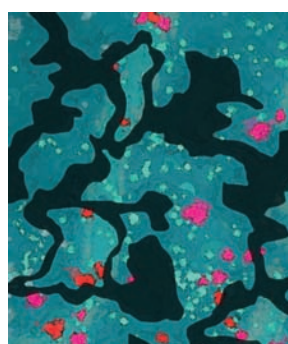
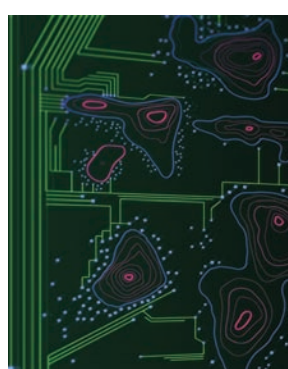
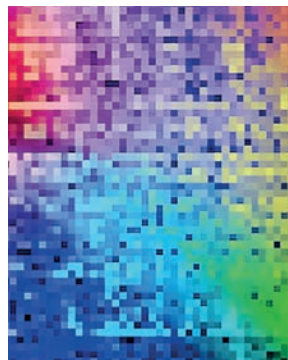
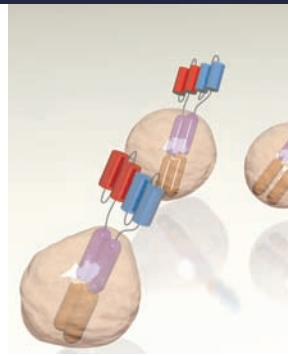
A.C. McCarter, G. Della Gatta, A. Melnick, E. Kim, C. Sha, Q. Wang, J.K. Nalamolu, Y. Liu, T.M. Keeley, R. Yan, M. Sun, R. Kodgule, N. Kunnath, A. Ambesi-Impiombato, R. Kuick, A. Rao, R.J.H. Ryan, B.L. Kee, L.C. Samuelson, M.C. Ostrowski, A.A. Ferrando, and M.Y. Chiang

Précis: Ets1 coregulates Notch transcriptional program in T cells and is essential for Notch-driven T-ALL but not intestinal homeostasis, suggesting its targeting in T-ALL as a less toxic alternative to Notch inhibition.

Apolipoprotein C2 - CD36 Promotes Leukemia Growth and Presents a Targetable Axis in Acute Myeloid Leukemia198

T. Zhang, J. Yang, V.P. Vaikari, J.S. Beckford, S. Wu, M. Akhtari, and H. Alachkar

Précis: Elevated APOC2 expression correlates with MLL-rearrangement and worse prognosis in AML. APOC2 promotes AML growth through CD36-dependent lipid metabolism, and blocking APOC2 or CD36 slows down AML progression in mice.





ON THE COVER

Multiple myeloma often relapses following CAR T cell therapy. The relapsing myeloma cells often lose or decrease the expression of the CAR-targeted antigen, suggesting antigen escape prevention may increase durability of the remission. In this issue, Eric Smith, Renier Brentjens and colleagues present approaches for simultaneously targeting BCMA and GPRC5D myeloma antigens by a single CART infusion. BCMA/GPRC5D dual-specific CAR T cells eliminate myeloma cells positive for both antigens, and protect mice from rechallenge with BCMA-negative myeloma. Among three orthogonal approaches, the best CAR T performance is achieved when BCMA and GPRC5D CARs are encoded by a bicistronic vector. The results pave the way to testing whether the dual-antigen CAR therapy would prevent antigen escape and extend the remission in patients with BCMA+ GPRC5D+ myeloma in clinical trials. For details, please see the article by Fernández de Larrea *et al.* on page 146 and the accompanying commentary by Simon and Riddell on page 130.



BLOOD CANCER DISCOVERY

1 (2)

Blood Cancer Discov 2020;1:127-213.

Updated version Access the most recent version of this article at:
<http://bloodcancerdiscov.aacrjournals.org/content/1/2>

E-mail alerts [Sign up to receive free email-alerts](#) related to this article or journal.

Reprints and Subscriptions To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions To request permission to re-use all or part of this article, use this link <http://bloodcancerdiscov.aacrjournals.org/content/1/2>. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.