

IN THIS ISSUE Highlighted research articles 1

IEWS In The Spotlight

A Novel Function of Sphingolipid Signaling via S1PR3 in Hematopoietic and Leukemic Stem Cells 3
C. Yang, M. Yamashita, and T. Suda

See article, p. 32

Epigenetic Trajectories of the Premalignant-to-Malignant Transition of Chronic Lymphocytic Leukemia 6
D. Rossi

See article, p. 54

In Focus

Viral Immunity and Vaccines in Hematologic Malignancies: Implications for COVID-19 9
M.V. Dhodapkar, K.M. Dhodapkar, and R. Ahmed

Cancer and COVID-19: On the Quest for Effective Vaccines ... 13
M. Kwok, E.F. Fritsch, and C.J. Wu

REVIEW **T-cell Acute Lymphoblastic Leukemia: A Roadmap to Targeted Therapies** 19
V. Cordo, J.C.G. van der Zwet, K. Canté-Barrett, R. Pieters, and J.P.P. Meijerink

RESEARCH ARTICLES **Sphingosine-1-Phosphate Receptor 3 Potentiates Inflammatory Programs in Normal and Leukemia Stem Cells to Promote Differentiation** 32
S.Z. Xie, K.B. Kaufmann, W. Wang, M. Chan-Seng-Yue, O.I. Gan, E. Laurenti, L. Garcia-Prat, S.-i. Takayanagi, S.W.K. Ng, C. Xu, A.G.X. Zeng, L. Jin, J. McLeod, E. Wagenblast, A. Mitchell, J.A. Kennedy, Q. Liu, H. Boutzen, M. Kleinau, J. Jargstorf,

G. Holmes, Y. Zhang, V. Voisin, G.D. Bader, J.C.Y. Wang, Y.A. Hannun, C. Luberto, T. Schroeder, M.D. Minden, and J.E. Dick

Précis: Proinflammatory lipid receptor S1RP3 drives myeloid differentiation in HSC as well as LSC and marks a specific subtype of less-primitive LSC, serving as a promising biomarker and therapeutic target for AML.

See commentary, p. 3

Preneoplastic Alterations Define CLL DNA Methylome and Persist through Disease Progression and Therapy 54

H. Kretzmer, A. Biran, N. Purroy, C.K. Lemvigh, K. Clement, M. Gruber, H. Gu, L. Rassenti, A.W. Mohammad, C. Lesnick, S.L. Slager, E. Braggio, T.D. Shanafelt, N.E. Kay, S.M. Fernandes, J.R. Brown, L. Wang, S. Li, K.J. Livak, D.S. Neuberg, S. Klages, B. Timmermann, T.J. Kipps, E. Campo, A. Gnirke, C.J. Wu, and A. Meissner

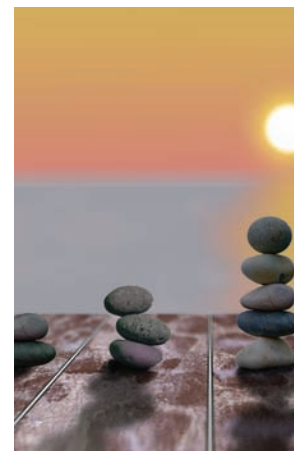
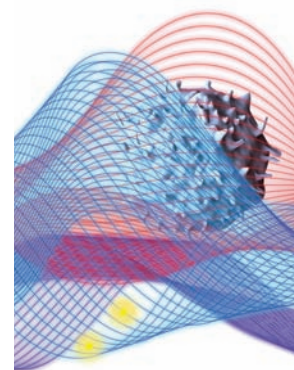
Précis: Longitudinal DNA methylome landscapes of normal, premalignant, and CLL cells reveal reprogramming at the earliest premalignant precursor stage, which is retained throughout clonal evolution and therapeutic interventions.

See commentary, p. 6

An Autochthonous Mouse Model of Myd88- and BCL2-Driven Diffuse Large B-cell Lymphoma Reveals Actionable Molecular Vulnerabilities 70

R. Flümman, T. Rehkämper, P. Nieper, P. Pfeiffer, A. Holzem, S. Klein, S. Bhatia, M. Kochanek, I. Kisis, B.W. Pelzer, H. Ahlert, J. Hauer, A. da Palma Guerreiro, J.A. Ryan, M. Reimann, A. Riabinska, J. Wiederstein, M. Krüger, M. Deckert, J. Altmüller, A.R. Klatt, L.P. Frenzel, L. Pasqualucci, W. Béguelin, A.M. Melnick, S. Sander, M. Montesinos-Rongen, A. Brunn, P. Lohneis, R. Büttner, H. Kashkar, A. Borkhardt, A. Letai, T. Persigehl, M. Peifer, C.A. Schmitt, H.C. Reinhardt, and G. Knittel

Précis: Myd88/BCL2-driven mouse model mimics the transcriptomic and morphologic features of human ABC-DLBCL and demonstrates that combination therapy blocking both BCL2 and PD-1 displays superior antilymphoma ability.

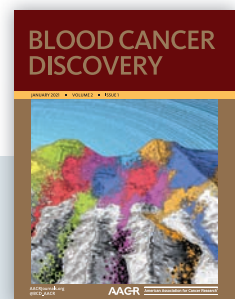


A Tumor Suppressor Enhancer of *PTEN* in T-cell Development and Leukemia . . . 92

L. Tottone, O. Lancho, J.-W. Loh, A. Singh, S. Kimura, J. Roels, A. Kuchmiy, S. Strubbe, M.A. Lawlor, V. da Silva-Diz, S. Luo, S. Gachet, C.A. García-Prieto, R. Hagelaar, M. Esteller, J.P.P. Meijerink, J. Soulier, T. Taghon, P. Van Vlierberghe, C.G. Mullighan, H. Khiabani, P.P. Rocha, and D. Herranz

Précis: Noncoding genetic region PE is a conserved hematopoietic-specific *PTEN* long-distance enhancer. Its deletion accelerates Notch-driven leukemia in mice and is recurrent in human T-ALL.

ON THE COVER Leukemia stem cell (LSC) plasticity in acute myeloid leukemia (AML) presents a major therapeutic challenge. In this issue, Stephanie Xie, John Dick, and colleagues characterize sphingosine-1-phosphate receptor 3 (S1PR3) as a plausible target in AML. Through extensive gene profiling in large AML patient datasets, the authors identify two AML subsets with different sphingolipid gene signature, responsiveness to the S1P prodrug fingolimod, and responsiveness to chemotherapy. S1PR3 expression on human HSC and LSC is induced by inflammatory cytokines and drives their myeloid differentiation in synergy with NF- κ B signaling. Genetic and pharmacologic interrogation demonstrates how S1PR3 activation can drive AML cells into a differentiated state. This study offers detailed mechanistic insights into interconnections between metabolic, inflammatory, and myeloid differentiation circuits in HSC and LSC, and identifies two AML patient subgroups with distinct chemosensitivity. For details, please see the article on page 32 and the accompanying commentary by Toshio Suda and colleagues on page 3.



BLOOD CANCER DISCOVERY

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