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THE DISTILLERY

This week in therapeutics

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Cancer				
Acute lymphoblastic leukemia (ALL)	Bromodomain containing 4 (BRD4); notch 1 (NOTCH1)	Mouse and cell culture studies suggest combined inhibition of BRD4 and NOTCH1 could help treat T cell ALL. γ-Secretase inhibitors that block NOTCH1 are being developed to treat cancers including T cell ALL but are known to have transient efficacy. In NOTCH1-dependent human T cell ALL lines chronically exposed to a γ-secretase inhibitor, a persistent subpopulation of cells sensitive to BRD4 inhibition was identified. In mice grafted with primary human T cell ALL, a γ-secretase inhibitor plus the BRD4 inhibitor JQ1 increased survival compared with either agent alone or vehicle. Next steps include evaluating combined inhibition of BRD4 and NOTCH1 in additional mouse models of primary T cell ALL and screening for additional epigenetic targets that could help circumvent resistance to NOTCH1-inhibiting therapies. GlaxoSmithKline plc has the bromodomain inhibitor GSK525762 in Phase I trials to treat cancer. At least three other companies have bromodomain inhibitors in Phase I testing to treat cancer. At least eight companies have γ-secretase inhibitors or other NOTCH1-inhibiting compounds in Phase II or earlier development to treat various cancers.	Patent application filed covering diagnostic and treatment methods in patients who have or are at risk for resistance to cancer therapy; available for licensing from the Broad Institute of MIT and Harvard	Knoechel, B. *et al. Nat. Genet.*; published online March 2, 2014; doi:10.1038/ng.2913 **Contact:** Bradley E. Bernstein, Massachusetts General Hospital and Harvard Medical School, Boston, Mass. e-mail: bernstein.bradley@mgh.harvard.edu **Contact:** Michelle A. Kelliher, University of Massachusetts Medical School, Worcester, Mass. e-mail: michelle.kelliher@umassmed.edu

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