

# A New Drug Bites AML

January 21, 2014

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Current chemotherapies for acute myeloid leukemia (AML) often do not provide long-term success in eradicating cancer cells. Targeted delivery of drugs to selectively destroy leukemic cells has led to some clinical success, including antibody-based drug therapy directed at the cell surface marker CD33 found on AML cells. However, clinical experience has shown that CD33 is a difficult antigen to target with antibody-drug conjugates. Harnessing the patient's immune system to target leukemic cells for destruction is now emerging as an alternative approach to treatment in AML. In a recent paper published in *Blood*, Dr. Roland Walter's laboratory in the Clinical Research Division and collaborators from the biotechnology company Amgen define the cellular determinants for activity of a novel bispecific T-cell engager (BiTE) antibody, AMG 330, against CD33-positive AML cells.

"Fred Hutchinson Cancer Research Center has a very long tradition in research on antibody-based therapy of AML, with one pursued avenue culminating in the development of the CD33 antibody-drug conjugate, gemtuzumab ozogamicin. We bring our expertise in defining mechanisms of action and resistance from gemtuzumab ozogamicin to the work on AMG 330," according to Dr. Walter. BiTE antibodies fuse two single-chain monoclonal antibodies, one that binds the cell surface protein CD3 present on cytotoxic T cells and a second that binds tumor cell antigens in order to redirect T cells to selectively lyse tumor cells (see figure). Encouraging clinical results using blinatumomab, a BiTE targeting the B cell surface protein CD19, against treatment-refractory acute lymphoblastic leukemia validates the development of BiTE antibodies to treat other cancers (Topp *et al.*, 2012). Dr. Walter states, "AMG 330 resembles blinatumomab except that the CD19-targeting part is replaced with a CD33-targeting part."

In this study, senior scientist Dr. George Laszlo and colleagues explored the cellular determinants for the activity of AMG 330 by using well-controlled AML cell lines in the presence of healthy donor T cells. The researchers engineered AML cell lines to express increasing levels of CD33, and found that AMG 330-induced cytotoxicity was related to the level of CD33 expression. This result suggests that CD33 expression levels on AML patients may be a limiting factor for drug efficacy. CD33 expression was unchanged on the cell surface after AMG 330 exposure, suggesting that long-term exposure to the BiTE antibody, as is clinically done with blinatumomab, does not decrease target protein expression. The researchers then examined if the presence of drug efflux transporters,

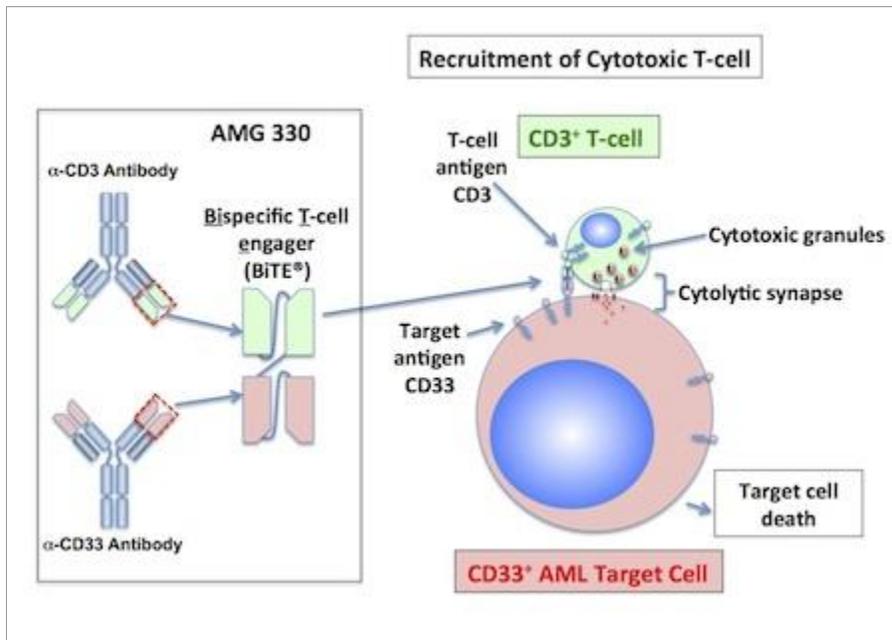
including ABC transporters, had an effect on AMG 330 toxicity levels. AMG 330 toxicity was not affected by the presence of ABC transporters, unlike gemtuzumab ozogamicin, which delivers a toxic payload to AML cells via internalization of a bivalent CD33 antibody.

Laszlo *et al.* then asked if AMG 330 activity could be affected by clinically available drugs that modify epigenetic regulators, such as panobinostat and azacitidine, which block histone deacetylases and DNA methyltransferase I, respectively. Both drugs increased CD33 expression on AML cells, and in turn increased sensitivity to AMG 330. The researchers then extended their studies to primary cells from AML patients, and again found that higher CD33 expression increases sensitivity to AMG 330.

Dr. Walter states that these studies are "the first that are focused on understanding the factors that are important for the activity of AMG 330. This information should contribute to our understanding as to which patients may be particularly susceptible (or resistant) to this therapeutic approach." Future studies in the Walter lab will expand this work to better understand the efficacy of AMG 330 on primary AML specimens.

[Laszlo GS, Gudgeon CJ, Harrington KH, Dell'aringa J, Newhall KJ, Means GD, Sinclair AM, Kischel R, Frankel SR, Walter RB](#). 2013. Blood. Cellular determinants for preclinical activity of a novel CD33/CD3 bispecific T-cell engager (BiTE) antibody, AMG 330, against human AML. *Blood*. Epub ahead of print, doi: 10.1182/blood-2013-09-527044.

See also: [Topp MS, Gökbüget N, Zugmaier G, Degenhard E, Goebeler ME, Klinger M, Neumann SA, Horst HA, Raff T, Viardot A, Stelljes M, Schaich M, Köhne-Volland R, Brüggemann M, Ottmann OG, Burmeister T, Baeuerle PA, Nagorsen D, Schmidt M, Einsele H, Riethmüller G, Kneba M, Hoelzer D, Kufer P, Bargou RC](#). 2012. Long-term follow-up of hematologic relapse-free survival in a phase 2 study of blinatumomab in patients with MRD in B-lineage ALL. *Blood* 120:5185-5187.



*Image provided by Dr. George Laszlo*

AMG 330, a bispecific T-cell engager (BiTE), fuses portions of antibodies specific for the CD3 antigen found on T-cells and the CD33 antigen found on AML cells. AMG 330 promotes T-cell-directed killing of CD33+ AML target cells.