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Biparatopic heavy chain antibodies (bi-hcAbs): fusion of two distinct CD38-specific nanobodies into a human IgG1 bi-hcAb results in potent CDC vs. myeloma cells

Kerstin Schütze, Julia Hambach, Katharina Petry, William Fumey, Birte Albrecht, Levin Schriewer, Jana Röckendorf, Stephan Menzel, Friedrich Haag, Catelijne Stortelers, Peter Bannas, Friedrich Koch-Nolte*

University Medical Center Hamburg-Eppendorf, Hamburg, Germany

* *Corresponding author, email: nolte@uke.de*

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Purpose/Objectives: The purpose of this study was to generate CD38-specific heavy chain antibodies (hcAbs) with improved complement dependent cytotoxicity (CDC) against multiple myeloma cells. Daratumumab is an effective therapeutic mAb targeting CD38, an ecto-enzyme overexpressed on multiple myeloma and other hematological malignancies. Patients that become refractory to daratumumab have myeloma cells expressing increased levels of complement inactivating proteins (CD55, CD59), suggesting that CDC is a mechanism of action of this mAb.

Materials/Methods: We fused the soluble variable domain (VHH or nanobody) of CD38-specific llama heavy chain antibodies (hcAbs) to the hinge-CH2-CH3 domains of human IgG1 (Fig. 1). In order to compare the CDC potency of daratumumab and nanobody-based hcAbs, we incubated CD38-expressing LP-1 myeloma and CA-46 Burkitt lymphoma cells with individual Abs or combinations of Abs in the presence of human serum as a source of complement and monitored cell death by flow cytometry.

Results: Monospecific and bispecific hcAbs were produced at high yield as highly soluble proteins by transiently-transfected HEK-cells. While daratumumab showed a moderate potency to induce CDC toward LP-1 or CA-46 cells, individual hcAbs showed only little if any CDC potency. In contrast, combinations of two hcAbs recognizing distinct epitopes of CD38 potently induced CDC. Similarly, combining daratumumab with a hcAb recognizing a non-overlapping epitope of CD38 markedly increased its CDC potency. Remarkably, bispecific hcAbs containing nanobodies that recognize two non-overlapping epitopes of CD38 displayed even higher CDC inducing potency than daratumumab.

Conclusion: Our results illustrate the therapeutic potential of chimeric nanobody-based human IgG1 heavy chain antibodies. The biparatopic CD38-specific hcAbs may represent alternatives to daratumumab for the treatment of hematological malignancies.

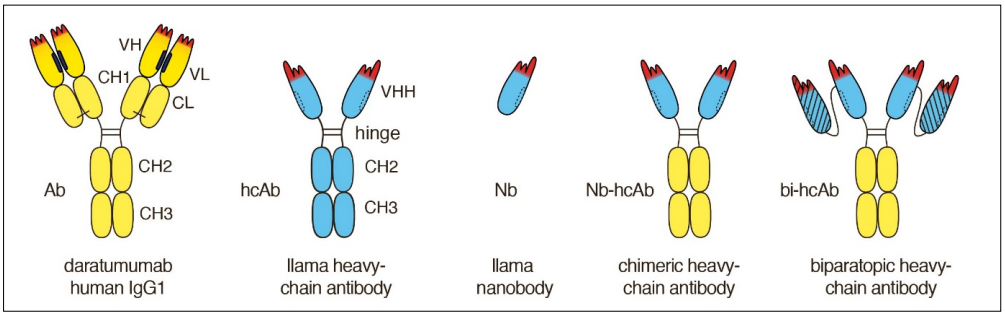

Figure 1: Generation of CD38-specific nanobody-based biparatopic human IgG1 hcAbs