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Domain-Exchanged Antibody with Potentiated Effector Functions

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We have designed a complete-antibody-like construct where the CL and CH1 domains of trastuzumab are exchanged for a pair of CH3 domains and efficient heterodimerization of the light and the heavy chain is achieved using "Knobs-into-Holes"strategy. The construct prepared in this way expressed at a high level in HEK293 system. Rational mutagenesis of the amino acid residues located at the interface between the variable domains and the exchanged CH3 domains was applied to significantly improve thermostability and solubility of the molecule. The domain-exchanged construct was able to bind to the surface of the strongly HER2/neu positive cell line SK-BR3 within less than 2-fold the affinity of trastuzumab, but could nevertheless incite a more potent T-cell activation in an ADCC assay. This could be explained by a more than 3-fold stronger binding to the FcRIIIa. The domain-exchanged antibody presents a novel class of engineered immunoglobulin molecules of therapeutic interest due to their potentiated engagement of the molecules that can elicit effector functions.

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