

POSTER PRESENTATION

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Targeting the Fc μ -receptor in chronic lymphocytic leukemia with a novel IgM-derived antibody-drug conjugate

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Fc-receptors (FcR) are widely expressed on cells of the immune system. Fc μ R is a transmembrane protein with an extracellular Ig-like domain homologous to the FcR for both IgA and IgM (Fc α / μ R) and the polymeric Ig receptor (pIgR). Fc μ R is expressed on CD19+B cells, CD4+/CD8+ T cells, and CD56+/CD3- NK cells. In addition, several groups have reported that Fc μ R is overexpressed in chronic lymphocytic leukemia (CLL) cells. Using immunofluorescence staining, we found that Fc μ R can rapidly uptake IgM, internalize it in specific vesicles and transport it through the endocytic pathway to the lysosomal compartment. Interestingly, aggregation of Fc μ R with IgM leads to rapid internalization of IgM (>80% internalized within 5 minutes) whereas mAb bound Fc μ R is not internalized. Overexpression on CLL cells and rapid internalization of Fc μ R represents a potential means of selectively delivering a cytotoxic agent into malignant cells. To this end, we engineered a protein scaffold derived from the CH2-CH3-CH4 IgM constant regions with a C-terminal selenocysteine that allows covalent conjugation of drugs or toxins to the protein scaffold. We verified that the scaffold also binds Fc μ R, is rapidly internalized and has a serum circulatory half-life comparable to IgM (~18hrs) in NOD/SCID/IL-2R γ null (NSG) mice. We then demonstrated that the scaffold, when conjugated to a cytotoxic small molecule, kills malignant B cells, but not normal T cells, from CLL patients *in vitro* and in NSG mice. These findings indicate that the rapid internalization of IgM-Fc μ R complexes can be exploited for therapeutic

purposes. Taken together, IgM-derived protein scaffold antibody-drug conjugates appear as promising treatment modalities for CLL and possibly other malignancies.

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