Skarzynski et al. Journal for ImmunoTherapy of Cancer 2013, 1(Suppl 1):P136
http://www.immunotherapyofcancer.org/content/1/S1/P136

Journal for ImmunoTherapy of Cancer

POSTER PRESENTATION Open Access

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

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From Society for Immunotherapy of Cancer 28th Annual Meeting
National Harbor, MD, USA. 8-10 November 2013

Fc-receptors (FcR) are widely expressed on cells of the immune system. FcμR is a transmembrane protein with an extracellular Ig-like domain homologous to the FcR for both IgA and IgM (Fcα/μR) and the polymeric Ig receptor (pIgR). FcμR is expressed on CD19+B cells, CD4+/CD8+ T cells, and CD56+/CD3- NK cells. In addition, several groups have reported that FcμR is overexpressed in chronic lymphocytic leukemia (CLL) cells. Using immunofluorescence staining, we found that FcμR can rapidly uptake IgM, internalize it in specific vesicles and transport it through the endocytic pathway to the lysosomal compartment. Interestingly, aggregation of FcμR with IgM leads to rapid internalization of IgM (>80% internalized within 5 minutes) whereas mAb bound FcμR is not internalized. Overexpression on CLL cells and rapid internalization of FcμR 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 FcμR, is rapidly internalized and has a serum circulatory half-life comparable to IgM (~18hrs) in NOD/SCID/IL-2Rγnull (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-FcμR 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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Published: 7 November 2013

doi:10.1186/2051-1426-1-S1-P136
Cite this article as: Skarzynski *et al.*: Targeting the Fcμ-receptor in chronic lymphocytic leukemia with a novel IgM-derived antibody-drug conjugate. *Journal for ImmunoTherapy of Cancer* 2013 **1**(Suppl 1):P136.

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