



Session PO.IM02.26 - Therapeutic Antibodies 4

5664 / 25 - A bispecific IgM antibody format for enhanced T cell dependent killing with minimal cytokine release

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📍 Virtual Meeting II: E-Posters



Presenter/Authors

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Disclosures

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Abstract

We have developed a novel T cell engaging bispecific antibody platform that utilizes the high avidity of IgM antibodies, but further combines this with the high affinity and specificity of IgG antibodies. By grafting the affinity matured binding domains of IgG antibodies onto the multimeric framework of an IgM antibody and fusing a CD3 binding single chain Fv domain to the J-chain, the resultant engineered IgM T cell bispecific antibody demonstrates strong binding to specific targets while limiting over-stimulation of engaged T cells. One of our bispecific IgM antibodies, IGM-2323, binds CD20 antigen with more than 1000 fold increased avidity and mediates complement dependent cytotoxicity (CDC) of CD20-expressing cells with greater than 100 fold higher potency when compared to the corresponding IgG bispecific. IGM-2323 also shows highly potent T cell dependent cytotoxicity, even on cells with very low cell surface expression of CD20 and on rituximab-resistant variants of Ramos cells. Significantly, IGM-2323 exhibits vastly reduced cytokine release *in vitro* and *in vivo*, with at least equivalent T cell dependent killing of CD20-expressing target cells, providing a potentially safer and more effective bispecific format than IgG-based T cell bispecifics. These data indicate that IgM-based bispecifics can induce T cell engagement and very potent cytotoxicity that can be dissociated from the cytokine release unlike what has been observed with other IgG-based bispecific antibodies. *In vivo* efficacy studies in humanized NSG mice indicated that doses as low as 3 µg/mouse cause complete B cell elimination. Similarly, bispecific IgM completely depletes circulating B cells in cynomolgus monkeys at doses of 300 µg per kg. Furthermore, in these primate studies, durable depletion of B cells in spleen and lymphoid tissues was noted without any observable adverse effects despite repeated doses at the highest dose tested, 25 mg/kg. Low levels of transiently increased circulating IL-6 and no increased levels of TNF-alpha and IFN-gamma were observed in these primate studies. These preclinical data demonstrate the potential for broad application of this novel modular IgM-based bispecific antibody format. A Phase I dose-escalation study of IGM-2323 is currently on-going in patients with relapsed/refractory Non-Hodgkin's Lymphoma.