IGM-2323: High Avidity IgM-based CD20 x CD3 Bispecific Antibody for Enhanced T-Cell Dependent Killing with Minimal Cytokine Release

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Background

- Bispecific T-cell engagers are emerging therapeutic modalities for treating hematological malignancies, especially tumors resistant to mAbs and CAR-T's
- Current bispecific antibodies are largely based on IgG-like scaffolds. Although some early success has been seen in the clinic, adverse events related to cytokine release remain a major concern with IgG-based bispecific antibodies
- IGM-2323 is an IgM-based bispecific that uses an anti-CD20 IgM to provide high avidity binding to CD20, an scFv fused to the N-terminus of J-chain to provide monovalent engagement of CD3 on T-cells, and human serum albumin (HSA) fused to the C-terminus of J-chain to improve pharmacokinetics
- Our preclinical data show highly effective complement dependent cytotoxicity (CDC) and T-cell dependent cellular cytotoxicity (TDCC) killing of tumor cells without associated cytokine release, for potentially larger therapeutic index
- Phase I clinical trial of IGM-2323 has been initiated in patients with Non-Hodgkins Lymphoma (NHL) in 2019 (ClinicalTrials.gov ID: NCT 04082936)

Bispecific IgM Format

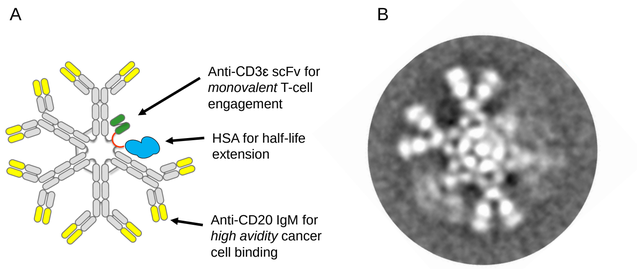


Figure 1.A. Schematic diagram of a bispecific IgM. For IGM-2323, the variable regions of IgM were designed to bind CD20 and the scFv fused to J-chain binds CD3.

Figure 1.B. Cryo-electron micrograph of bispecific IgM showing the asymmetric structure of the pentameric IgM with the J-chain fusion.

High Avidity Binding of Antigen by anti-CD20 IgM

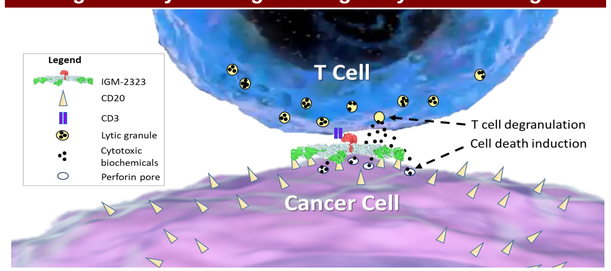


Figure 2. Schematic diagram of T-cell engagement by B-cell bound IGM-2323. We believe that the bispecific IgM format allows simultaneous engagement of multiple antigens on the target cell surface and engages a single CD3 on T-cells for each IgM, resulting in a more "physiological" immune synapse compared to BiTEs or bispecific IgG format.

Superior Binding of Bispecific IgM vs IgG

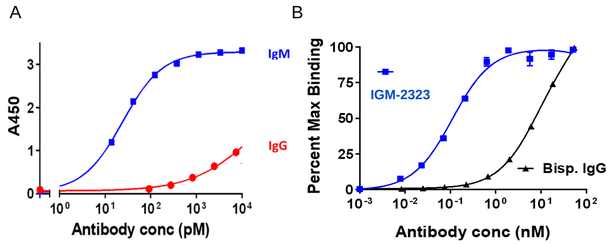


Figure 3.A. IGM-2323 or IgG with identical CD20 binding variable domains to CD20 ECD coated on a plate at 10 μg/mL. Highly avid IgM allows >1000x more potent binding than IgG.

Figure 3.B Binding of IGM-2323 or corresponding bispecific IgG (with CD20 and CD3 binding units) to CD20 expressing Ramos cells. IgM antibodies bind cell surface CD20 more than 100x better than the bispecific IgG with apparent K_d of 0.11 nM vs 8.1 nM.

IGM-2323 Kills Cell Lines with Low CD20 Expression and Cell Line Selected for Rituximab Resistance

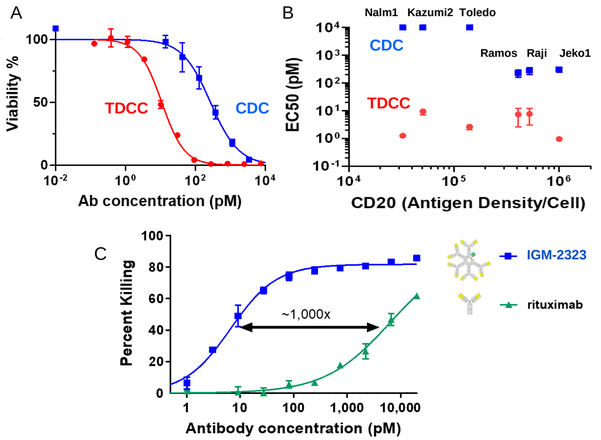


Figure 4. A) TDCC is more potent than CDC in vitro. T cell dependent cellular cytotoxicity (TDCC) of Ramos cells using CD8+ T-cells at effector:target ratio of 5;1 for 48 hrs exhibits more potent killing (EC50=8.6 pM), whereas complement-dependent cytotoxicity of IGM-2323 on Ramos cells indicates an EC50 of 250 pM

Figure 4. B) Comparison of CDC and TDCC activity on various cell lines. Potent TDCC based killing of low CD20 expressing cell lines was observed. Less potency of CDC on those cells.

Figure 4. C) Comparison of cell killing activity of rituximab resistant cells in human PBMCs with 10% serum. A rituximab resistant clone of Ramos cells was created by serial outgrowth of CDC survivors over six cycles. Bispecific IgM IGM-2323 is able to show ~1000x better killing of this rituximab resistant cell line compared to rituximab with EC50 of 6.6 pM vs 6350 pM.

Bispecific IgM Shows Low Cytokine Release In Vitro

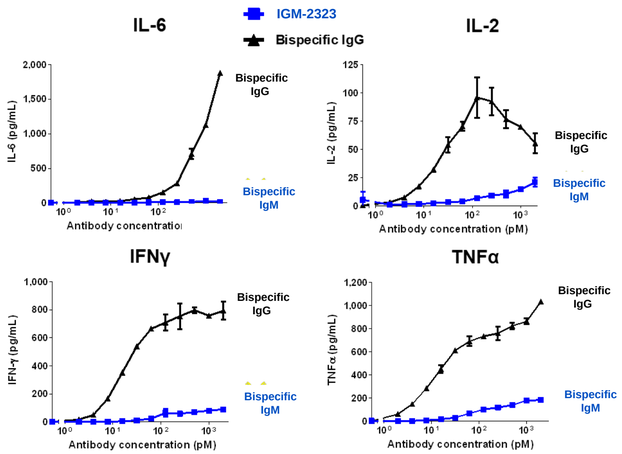


Figure 5. In vitro comparison of four cytokines elevated in "cytokine release syndrome" observed with bispecific IgG's. IGM-2323 or a bispecific IgG with the same CD20 and CD3 binding units were incubated with human PBMCs from mixed donors for 48 hours and the supernatant assayed for cytokines using flow cytometry. Levels of cytokine release observed for IGM-2323 are orders of magnitude lower than that for the corresponding bispecific IgG indicating potential for greater therapeutic window using bispecific IgM T cell engagers.

IGM-2323,-2324 Show Efficacy In Cynomolgus Monkeys

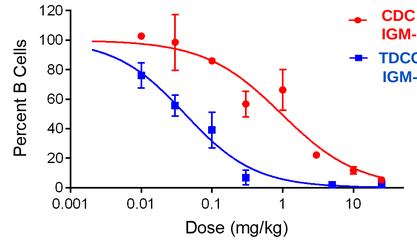
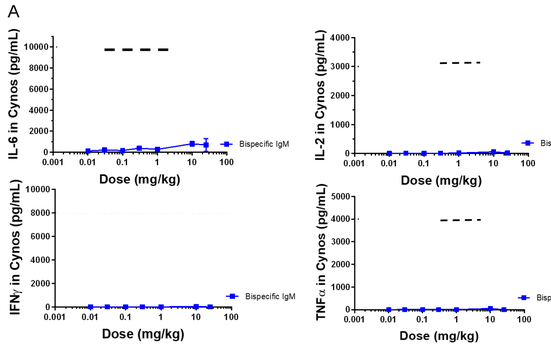


Figure 6. Depletion of peripheral B-cells upon treatment of Cynomolgus monkeys with a single dose of either IGM-2323 (non-cyno cross-reactive) or IGM-2324 (cynomolgus monkey CD3 cross-reactive scFv). The dose response curves indicate the bispecific IgM IGM-2324 with dual mechanism of B-cell killing (both CDC and TDCC), has an EC50 of 0.04 mg/kg vs IGM-2323 which only has CDC based B-cell killing and shows a roughly 25x higher EC50 of 0.94 mg/kg for B-cell depletion at 24 hours post administration.

IGM-2324 Shows Minimal Elevation of Cytokines in Cynomolgus Monkey Studies



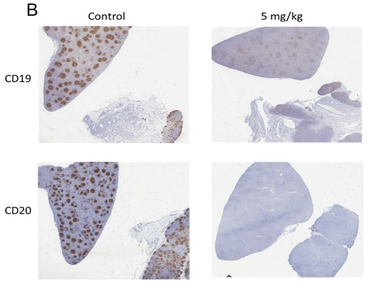


Figure 7.A. Cytokine levels were measured in a GLP toxicology study conducted in Cynomolgus monkeys with IGM-2324. Minimal elevation of cytokines was observed at the maximal tested dose of 25 mg/kg in comparison to reported data (dotted lines) for competing bispecific IgG's at ≤ 3 mg/kg.

Figure 7.B. Immunohistochemistry to detect CD19 and CD20 positive B cells in non-human primate spleen and mesenteric lymph nodes from animals administered with IGM-2324.

Summary

- We have developed a novel bispecific IgM platform that allows highly avid engagement of tumor antigens with monovalent engagement of CD3 on T cells.
- Bispecific IGM-2323 exhibits 100x greater binding to CD20 antigen on a tumor cell line compared to a corresponding bispecific IgG
- Highly potent CDC and TDCC based killing of tumor cell lines is demonstrated in vitro together with potent killing of rituximab resistant cells
- Importantly, TDCC activity of IGM-2323 does not result in excessive in vitro cytokine release, commonly associated with CRS in clinical trials with other bispecific mAbs or CART therapy.
- IGM-2323 has potent activity in vivo in NSG mice (data not shown) as well as in cynomolgus monkeys with durable depletion from spleen and lymph nodes.
- Very low cytokine release, durable depletion of B-cells in cyno monkeys and potent killing of rituximab resistant cells supports clinical development of IGM-2323 as a bispecific IgM to potentially treat Non-Hodgkin's lymphoma patients.
- Phase I clinical trial is currently in progress. ClinicalTrials.gov ID: NCT 04082936

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