et al. Molecular Immunology 2006 (43) 763–771) which is also believed to be linked to the small size of the BiTE® format. If size matters, this would suggest that larger molecules such as intact IgG would be too large to form effective cytolytic synapses. The CD3xCD19 BiTE®, blinatumomab, has demonstrated remarkable clinical efficacy in refractory non-Hodgkin lymphoma and acute lymphatic leukemia patients (Bargou et al. 2008 Science 321:974). Although the CD3xCD19 BiTE® displays very efficient tumor cell lysis at low levels in vitro, administration of this bispecific format to patients is associated with significant challenges. Due to their small size, BiTE®s are rapidly cleared from the circulation and dosing of patients thus requires continuous infusion. As the dosing regimen has an overall duration of more than 2 months, this treatment has a significant impact on the quality of life of the patients.

[0004] There thus remains a need for effective full length bispecific T cell engaging IgG molecules in eradicating aberrant cells that combine a long circulatory half-life upon intravenous administration without the need for continuous infusion without being immunogenic and with only limited side effects.

SUMMARY

[0004a] In one aspect, there is provided a bispecific IgG antibody, wherein said bispecific IgG antibody comprises one arm that specifically recognizes CLEC12A or a functional equivalent thereof, and a second arm that specifically recognizes an antigen on immune effector cells capable of recruiting such cells to an aberrant cell expressing CLEC12A or said functional equivalent.

[0004b] In another aspect, there is provided a method for producing a bispecific IgG antibody as defined herein from a single cell, wherein said bispecific IgG antibody comprises two CH3 domains that are capable of forming an interface, said method comprising providing:

- a cell having a) a first nucleic acid sequence encoding a IgG heavy chain that specifically recognizes CLEC12A and that contains a 1st CH3 domain, and b) a second nucleic acid sequence encoding a IgG heavy chain that specifically recognizes an antigen on immune effector cells, preferably CD3, and that contains a 2nd CH3 domain, wherein said nucleic acid sequences are provided with means for preferential pairing of said 1st and 2nd CH3 domains, said method further comprising the step of culturing said cell and allowing for expression of said two nucleic acid sequences and harvesting said bispecific IgG antibody from the culture.

[0004c] In another aspect, there is provided an antibody obtainable by a method as defined herein.

[0004d] In another aspect, there is provided a pharmaceutical composition comprising a bispecific IgG antibody as defined herein and a pharmaceutically acceptable carrier.

[0004e] In another aspect, there is provided a bispecific IgG antibody as defined herein for use as a pharmaceutical in the treatment of myelodysplastic syndrome (MDS), chronic myelogenous leukemia (CML) or preferably acute myeloid leukemia (AML).

[0004f] In another aspect, there is provided use of a bispecific IgG antibody as defined herein in the preparation of a medicament for the treatment or prevention of myelodysplastic syndrome (MDS), chronic myelogenous leukemia (CML) or preferably acute myeloid leukemia (AML).

BRIEF DESCRIPTION OF THE FIGURES

[0005] FIG. 1: CLEC12A and related sequences.

[0006] FIG. 2: T-cell activation by various antibodies: monoclonal bivalent CD3 IgG, bispecific CD3XCLEC12 IgG, bispecific CD3xisotype control IgG, monoclonal bivalent CLEC12A IgG, monoclonal bivalent isotype control IgG.

[0007] FIG. 3: Specific lysis of HL60 cells by CD3XCLEC12A bispecific IgG and control antibodies.

[0008] FIG. 4: Specific lysis of HL60 cells by CD3XCLEC12A bispecific IgG and control antibodies (E:T ratios).

[0009] FIG. 5: Specific lysis of HL60 cells with several CD3XCLEC12A bispecific IgG molecules consisting of various CLEC12A arms & fixed CD3 arm, and control antibodies.

[0010] FIG. 6: Specific lysis of HL60 cells with CD3XCLEC12A bispecific IgG in combination with Fc silencing (DM=Double mutant; TM= triple mutant; WT=wildtype, no Fc silencing).

[0011] FIG. 7: Fc silencing does not affect FcRn binding.

[0012] FIG. 8: CD3xCLEC12A bsAb target specific induction of T cell proliferation.

[0013] FIG. 9: CD8+ T cell compartment of AML patients compared to healthy donors.

[0014] FIG. 10: Specific CD3xCLEC12A DM-Fc induced T cell activation and HL60 tumor cell lysis by AML patient T cells.

[0015] FIG. 11: Specific lysis of AML blasts by autologous AML patient T cells.

[0016] FIG. 12: Specific monocyte lysis by patient T cells.

[0017] FIG. 13: Fc silencing significantly eliminates bystander cell cytokine release.

[0018] FIG. 14A: FACS staining anti-CD3 antibodies on HPB-ALL cells

[0019] FIG. 14B: Plate bound IgG, T cells labeled with CFSE, read out at day 5 by FACS

[0020] FIG 15:HL60 cytotoxicity assay

[0021] FIG 16: FACS staining anti-CLEC12A antibodies on HL60 cells

[0022] FIG. 17: HL60 cytotoxicity assay

[0023] FIG 18: FACS analysis

[0024] FIG 19: HL60 cytotoxicity assay

[0025] FIG 20: VH sequences of CD3-specific and CLEC12A-specific Fab arms. VL sequence of O12 common light chain. CDR sequences are bold and underlined.

~~SUMMARY~~ DISCLOSURE OF THE INVENTION

[0026] The present invention describes a fully human IgG bispecific full length antibody for the treatment of AML. One arm of the antibody binds an epitope on immune effector cells, preferably CD3, whilst the other arm targets CLEC12A, a myeloid cell specific surface target that is expressed in 90-95% of de novo and relapsed AML patients. CLEC12A is expressed on AML leukemic stem cells, but not on normal haematopoietic cells. Unlike CD33, CLEC12A is not expressed on erythroid precursors or megakaryocytes, so the CD3xCLEC12A bispecific IgG1 antibody of the present invention should not induce platelet or red blood cell depletion.Experiments with bone marrow cell colonies have shown that depletion of CLEC12A+ cells in normal bone marrow does not affect the myeloid lineages that give rise to platelets and red blood cells. A CD3xCLEC12A bispecific IgG antibody according to the present invention in a preferred embodiment contains a modified Fc region so as to reduce non-specific immune activation resulting from engagement of T cells and FcγR expressing cells within PBMC. Based