wherein one site binds a surface antigen on a target cell and the other site binds an effector cell surface antigen.

Nevertheless, improvements in effector cell redirecting antibody-based therapeutics are still needed, particularly relating to the therapeutic window. The therapeutic window is defined as the range in concentration of a drug that exerts therapeutic efficacy with no or limited toxicity observed. (Handbook of Pharmacogenomics and Stratified Medicine, 2014). The aim of any therapy is to reach a dose where efficacy is seen in all patients, with no or manageable side effects in any of the patients (Principles of Clinical Pharmacology (Third Edition), 2012). To broaden a bispecific antibody's therapeutic window, the concentration of a drug that gives half-maximal therapeutic response (EC50) can be decreased (improved efficacy), and/or the concentration that exerts toxic effects can be increased (improved on-target specificity).

Aiming to target a larger therapeutic window in comparison to other approved or candidate medicines for CD38-overexpressing cancers, such as multiple myeloma, the inventors have set out to provide improved effector cell redirecting antibody-based therapeutics, that specifically act on the tumor cells. Nevertheless, while it has been shown that monoclonal antibodies that binds CD38, such as dararumumab, may be used in combination with CD47-blocking scFv genetically fused in tandem to a CD20-targeting scFv to enhance phagocytosis of cancer cells by blocking the CD47/SIRPα signal (van Bommel, P. E. et al. (2017) CD20-selective inhibition of CD47-SIRPa "don't eat me" signaling with a bispecific antibody-derivative enhances the anticancer activity of daratumumab, alemtuzumab and obinutuzumab. ONCOIMMUNOLOGY, vol. 7, no. 2, 1 - 8), the possibility to block the CD47-SIRPα interaction selectively in CD38 expressing cancer cells, still remains an unmet need.

Summary

In one aspect, provided herein is a bispecific antibody comprising at least two binding portions, at least one of which binds to human CD38 and at least one of which binds to human CD47.

In another aspect, provided herein is the bispecific antibody as described herein, for use as a medicament.

In another aspect, provided herein is use of the bispecific antibody as described herein in the manufacture of a medicament for treating multiple myeloma, acute lymphoblastic leukemia, chronic lymphocytic leukemia, acute myeloid leukemia, lymphoma, breast cancer such as Her2+ breast cancer, prostate

cancer, cervival cancer, germinal center B-cell lympohoma or B-cell acute lymphoblastic leukemia, Chronic lymphocytic leukemia (CLL), Myelodisplastic syndrome (MDS), Non-Hodgkin lymphoma, diffuse large B-cell lymphoma, non small cell lung cancer (NSCLC), Hepatocellular carcinoma (HCC), High-grade serous ovarian carcinoma, peritoneal cancer.

In another aspect, provided herein is an epitope on the human CD38 extracellular domain which is bound by the bispecific antibody as described herein.

In another aspect, provided herein is an epitope on the human CD47 extracellular domain which is bound by the bispecific antibody as described herein.

In another aspect, provided herein is an isolated nucleic acid encoding the bispecific antibody as described herein.

In yet another aspect, provided herein is a host cell comprising the isolated nucleic acid as described herein.

Detailed Description

The present invention relates to a bispecific antibody comprising at least two binding portions, at least one of which binds to human CD38 and at least one of which binds to human CD47.

The present invention also relates to a bispecific antibody comprising at least one binding portion which binds to human CD47 and at least two binding portions which bind to human CD38.

The present invention also relates to a bispecific antibody comprising at least one binding portion which binds to human CD47 and at least two binding portions which bind to human CD38, wherein the at least two CD38 binding portions are monoparatopic.