Immunologically Discernible Cell Surface Variants for Use in Cell Therapy

The present invention relates to the use of cells having a mutant but functional cell surface protein in medical applications wherein selective depletion or enrichment of cell populations is desirable. Mutant but functional cell surface proteins may be introduced into cells by gene editing methods including homology directed repair of DNA double strand breaks, in particular during CRISPR/Cas gene editing, or by the use of base editors. The invention further relates to an agent and a method for selective depletion of edited cells in vivo.

Cellular therapy is very powerful therapy option, but often associated with severe unwanted side effects. Transgenes and/or genetic engineering of the transferred cells can cause malignant transformation. Transfer of CAR-T cells can lead to severe on- and off-target effects (cytokine release syndrome) and transfer of allogeneic T cells can cause graft versus host disease (GvHD). The success of cellular therapy in oncology will likely boost cell therapies for other indications, including non-malignant diseases. To increase the safety of cellular therapies, particularly if used in the treatment of non-lethal diseases, it is important to ensure that transferred cells remain safe for years after transfer. In instances where severe unwanted side effects develop, a possibility to selectively deplete the transferred cells via a "safety or kill switch" would significantly increase the safety of cellular therapy.

The problem underlying the present invention is to provide a system that serves to permanently mark and track cells and allows the selective depletion of the marked or unmarked cells in vitro or in vivo. These problems are solved by the subject-matter of the independent claims.

Summary

In one aspect, the present disclosure refers to a use of a human hematopoietic cell, expressing a first isoform of a surface protein, wherein said first isoform of said surface protein is functionally indistinguishable, but immunologically distinguishable from a second isoform of said surface protein, in the manufacture of a medicament for treating a medical condition selected from the group consisting of (i) a hematopoietic disorder, (ii) a malignant hematopoietic disease, (iii) a non-malignant hematopoietic disease, (iv) Graft-versus-host disease in a human patient having cells expressing said second isoform of said surface protein, wherein said cell expressing the first isoform of the surface protein are to be administered prior to, concomitant with, or after specific ablation of cells expressing said second isoform of said surface protein, wherein said ablation is performed by administration to said patient of an antibody, wherein said antibody is specifically reactive to said second isoform but not to said first isoform of said cell surface protein, and wherein said first isoform is obtained *ex vivo* by changing a sequence encoding said surface protein gene in the patient's native genomic DNA by gene editing so as to obtain a first isoform is having an insertion, deletion and/or substitution of 1, 2, 3, 4 or 5 amino acids in the amino acid sequence compared to said second isoform of said surface protein.

Description

A first aspect of the invention relates to a mammalian cell, expressing a first isoform of a surface protein, wherein said first isoform of said surface protein is functionally indistinguishable, but immunologically distinguishable from a second isoform of said surface protein, for use in a medical treatment of a patient having cells expressing said second form of said surface protein.

The expression "immunologically distinguishable" refers to a first and a second isoform of the surface protein that can be distinguished by a ligand specifically binding to either the first or the second isoform.

In the context of the present specification, the expression "specific binding" refers to binding with a dissociation constant $K_D \leq 10$ E -7.

In the context of the present specification, the expression "ligand" relates to an antibody or an antibody-like molecule. The antibody or antibody-like molecule may be coupled to another molecule (e.g. in an immuno toxin) or may be present on the surface of a cell, in particular an immune cell.

In the context of the present specification, the term "antibody" is used in its meaning known in the art of cell biology and immunology; it refers to whole antibodies including but not limited to immunoglobulin type G (IgG), type A (IgA), type D (IgD), type E (IgE) or type M (IgM), any antigen binding fragment or single chains thereof and related or derived constructs. A whole antibody is a glycoprotein comprising at least two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds. Each heavy chain is comprised of a heavy chain variable region (VH) and a heavy

Claims

1. Use of a human hematopoietic cell, expressing a first isoform of a surface protein, wherein said first isoform of said surface protein is functionally indistinguishable, but immunologically distinguishable from a second isoform of said surface protein, in the manufacture of a medicament for treating a medical condition selected from the group consisting of (i) a hematopoietic disorder, (ii) a malignant hematopoietic disease, (iii) a non-malignant hematopoietic disease, (iv) Graft-versus-host disease in a human patient having cells expressing said second isoform of said surface protein, wherein said cell expressing the first isoform of the surface protein are to be administered prior to, concomitant with, or after specific ablation of cells expressing said second isoform of said surface protein, wherein said ablation is performed by administration to said patient of an antibody, wherein said antibody is specifically reactive to said second isoform but not to said first isoform of said cell surface protein, and wherein said first isoform is obtained *ex vivo* by changing a sequence encoding said surface protein gene in the patient's native genomic DNA by gene editing so as to obtain a first isoform is having an insertion, deletion and/or substitution of 1, 2, 3, 4 or 5 amino acids in the amino acid sequence compared to said second isoform of said surface protein.

2. The use according to claim 1, wherein said surface protein is selected from CD1a, CD1b, CD1c, CD1d, CD1e, CD2, CD3, CD3d, CD3e, CD3g, CD4, CD5, CD6, CD7, CD8a, CD8b, CD9, CD10, CD11a, CD11b, CD11c, CD11d, CDwl2, CD13, CD14, CD15, CD15u, CD15s, CD15su, CD16, CD16b, CD17, CD18, CD19, CD20, CD21, CD22, CD23, CD24, CD25, CD26, CD27, CD28, CD29, CD30, CD31, CD32, CD33, CD34, CD35, CD36, CD37, CD38, CD39, CD40, CD41, CD42a, CD42b, CD42c, CD42d, CD43, CD44, CD45, CD45RA, CD45RB, CD45RC, CD45RO, CD46, CD47, CD48, CD49a, CD49b, CD49c, CD49d, CD49e, CD49f, CD50, CD51, CD52, CD53, CD54, CD55, CD56, CD57, CD58, CD59, CD60a, CD60b, CD60c, CD61, CD62E, CD62L, CD62P, CD63, CD64, CD65, CD65s, CD66a, CD66b, CD66c, CD66d, CD66e, CD66f, CD68, CD69, CD70, CD71, CD72, CD73, CD74, CD75, CD75s, CD77, CD79a, CD79b, CD80, CD81, CD82, CD83, CD84, CD85a, CD85d, CD85j, CD85k, CD86, CD87, CD88, CD89, CD90, CD91, CD92, CD93, CD94, CD95, CD96, CD97, CD98, CD99, CD99R, CD100, CD101, CD102, CD103, CD104, CD105, CD106, CD107a, CD107b, CD108, CD109, CD110, CD111, CD112, CD113, CD114, CD115, CD116, CD117, CD118, CD119, CD120a, CD120b, CD121a, CD121b, CD122, CD123, CD124, CD125, CD126, CD127, CD129, CD130, CD131, CD132, CD133, CD134, CD135, CD136, CD137, CD138, CD139, CD140a, CD140b, CD141, CD142, CD143, CD144, CDw145, CD146, CD147, CD148, CDw149, CD150, CD151, CD152, CD153, CD154, CD155, CD156a, CD156b, CD156c, CD157, CD158e, CD158i, CD158k, CD159a, CD159c, CD160, CD161, CD162, CD163, CD164, CD165, CD166, CD167a, CD167b, CD168, CD169, CD170, CD171, CD172a, CD172b, CD172g, CD173, CD174, CD175, CD175s, CD176, CD177, CD178, CD179a, CD179b, CD180, CD181, CD182, CD183, CD184, CD185, CD186, CD191, CD192, CD193, CD194, CD195, CD196, CD197, CDw198, CD199, CD200, CD201, CD202b, CD203c, CD204, CD205, CD206, CD207, CD208, CD209, CD210, CDw210b, CD212, CD213a1, CD213a2, CD215, CD217a, CD218a, CD218b, CD220, CD221, CD222, CD223,

CD224, CD225, CD226, CD227, CD228, CD229, CD230, CD231, CD232, CD233, CD234, CD235a, CD235b, CD236, CD236R, CD238, CD239, CD240CE, CD240DCE, CD240D, CD241, CD242, CD243, CD244, CD245, CD246, CD247, CD248, CD249, CD252, CD253, CD254, CD256, CD266, CD267, CD268, CD269, CD270, CD271, CD272, CD273, CD274, CD275, CD276, CD277, CD278, CD279, CD280, CD281, CD282, CD283, CD284, CD286, CD289, CD290, CD292, CDw293, CD294, CD295, CD296, CD297, CD298, CD299, CD300a, CD300c, CD300e, CD301, CD302, CD303, CD304, CD305, CD306, CD307a, CD307b, CD307c, CD307d, CD307e, CD308, CD309, CD312, CD314, CD315, CD316, CD317, CD318, CD319, CD320, CD321, CD322, CD324, CD325, CD326, CD327, CD328, CD329, CD331, CD332, CD333, CD334, CD335, CD336, CD337, CD338, CD339, CD340, CD344, CD349, CD350, CD351, CD352, CD353, CD354, CD355, CD357, CD358, CD360, CD361, CD362, CD363, CD364, CD365, CD366, CD367, CD368, CD369, CD370, CD371, BCMA, an Immunoglobulin light chain (lambda or kappa), a HLA protein and β2-microglobulin,

in particular wherein said surface protein is selected from CD2, CD3, CD4, CD5, CD8, CD19, CD20, CD22, CD23, CD33, CD34, CD90, CD45, CD123, BCMA, an Immunoglobulin light chain (lambda or kappa), a HLA protein and β2- microglobulin.

3. The use according to any one of the preceding claims, wherein said first isoform is not encoded in the patient's native genomic DNA.

4. The use according to any one of the preceding claims, wherein said insertion, deletion and/or substitution is located in the extracellular portion of said first surface protein, particularly in an extracellular loop.

5. The use according to any one of the above claims, wherein said human hematopoietic cell is selected from the group consisting of a hematopoietic stem cell, a CD4+ T cell, a CD8+ T cell, a memory T cell, a regulatory T cell (T reg), a natural killer cell (NK), an innate lymphoid cell (ILC), a dendritic cell (DC), a B-lymphocyte, a mucosal-associated invariant T cell (MAIT) and a gamma delta T cell (γδ T), in particular a hematopoietic stem cell or a T cell.

6. The use according to any one of the above claims, wherein said medical condition is graft-versus-host disease caused by hematopoietic stem cell transplantation.