

[CLAIMS]

[Claim 1]

A hypoimmunogenic human cell

- (1) lacking an endogenous gene encoding an α chain of human leukocyte antigen (HLA) class Ia,
- (2) lacking an endogenous gene encoding HLA class II or an expression regulator thereof,
- (3) comprising an exogenous gene encoding an α chain of HLA class Ib,
- (4) comprising an exogenous gene encoding human PD-L1,
- (5) comprising an exogenous gene encoding human PD-L2, and
- (6) comprising an exogenous gene encoding human β 2 microglobulin.

[Claim 2]

- The cell according to claim 1, wherein the cell does not express endogenous HLA class Ib on a cell surface.

[Claim 3]

- The cell according to claim 1 or 2, wherein the endogenous gene encoding the α chain of the HLA class Ia comprises an endogenous gene encoding an α chain of HLA-A, an endogenous gene encoding an α chain of HLA-B, and an endogenous gene encoding an α chain of HLA-C.

[Claim 4]

- The cell according to any one of claims 1 to 3, wherein the endogenous gene encoding the HLA class II or an expression regulator thereof comprises the following (a) or (b):
 - (a) an endogenous gene encoding an α chain and/or a β chain of HLA-DP, an endogenous gene encoding an α chain and/or a β chain of HLA-DQ, an endogenous gene encoding an α chain and/or a β chain of HLA-DR, an endogenous gene encoding an α chain and/or a β chain of HLA-DM, and an endogenous gene encoding an α chain and/or a β chain of HLA-DO,
 - (b) an endogenous gene encoding human RFXANK, an endogenous gene encoding human RFX5, an endogenous gene encoding human RFXAP, and an endogenous gene encoding human CIITA.

[Claim 5]

The cell according to any one of claims 1 to 4, wherein the exogenous gene encoding the α chain of the HLA class Ib comprises an exogenous gene encoding an α chain of HLA-E and/or
5 an exogenous gene encoding an α chain of HLA-G.

[Claim 6]

The cell according to any one of claims 1 to 5, comprising (7) a suicide gene.

[Claim 7]

10 The cell according to any one of claims 1 to 6, wherein the site containing the exogenous gene or suicide gene is a safe harbor region of the genome.

[Claim 8]

The cell according to claim 7, wherein the safe harbor
15 region is an AAVS1 region, a CCR5 region, or a ROSA26 region.

[Claim 9]

The cell according to any one of claims 1 to 8, wherein the hypoinmunogenic human cell is a pluripotent stem cell or a differentiated cell thereof.

20 [Claim 10]

A method for producing a hypoinmunogenic human cell, comprising the following steps:

- (i) a step of deleting an endogenous gene encoding an α chain of HLA class Ia of a human parental cell,
- 25 (ii) a step of deleting an endogenous gene encoding HLA class II or an expression regulator thereof from the human parental cell,
- (iii) a step of introducing an exogenous gene encoding an α chain of HLA class Ib into the human parental cell,
- 30 (iv) a step of introducing an exogenous gene encoding human PD-L1 into the human parental cell,
- (v) a step of introducing an exogenous gene encoding human PD-L2 into the human parental cell, and
- (vi) a step of introducing an exogenous gene encoding human β 2
35 microglobulin into the human parental cell.

[Claim 11]

The method according to claim 10, wherein the hypoimmunogenic human cell does not express endogenous HLA class Ib on a cell surface.

5 [Claim 12]

The method according to claim 10 or 11, wherein the endogenous gene encoding the α chain of the HLA class Ia comprises an endogenous gene encoding an α chain of HLA-A, an endogenous gene encoding an α chain of HLA-B, and an endogenous
10 gene encoding an α chain of HLA-C.

[Claim 13]

The method according to any one of claims 10 to 12, wherein the endogenous gene encoding HLA class II or an expression regulator thereof comprises the following (a) or
15 (b):

(a) an endogenous gene encoding an α chain and/or a β chain of HLA-DP, an endogenous gene encoding an α chain and/or a β chain of HLA-DQ, an endogenous gene encoding an α chain and/or a β chain of HLA-DR, an endogenous gene encoding an α chain and/or
20 a β chain of HLA-DM, and an endogenous gene encoding an α chain and/or a β chain of HLA-DO,

(b) an endogenous gene encoding human RFXANK, an endogenous gene encoding human RFX5, an endogenous gene encoding human RFXAP, and an endogenous gene encoding human CIITA.

25 [Claim 14]

The method according to any one of claims 10 to 13, wherein the exogenous gene encoding the α chain of the HLA class Ib comprises an exogenous gene encoding an α chain of HLA-E and/or an exogenous gene encoding an α chain of HLA-G.

30 [Claim 15]

The method according to any one of claims 10 to 14, further comprising the following step:

(vii) a step of introducing a suicide gene into the human parental cell.

35 [Claim 16]

The method according to any one of claims 10 to 15,
wherein the site into which the exogenous gene or suicide gene
is introduced is a safe harbor region of the genome.

[Claim 17]

5 The method according to claim 16, wherein the safe harbor
region is an AAVS1 region, a CCR5 region, or a ROSA26 region.

[Claim 18]

 The method according to any one of claims 10 to 17,
wherein the human parental cell is a pluripotent stem cell or a
10 differentiated cell thereof.