METHODS AND COMPOSITIONS FOR CELLULAR THERAPY

CROSS-REFERENCE

[0001] This application claims the benefit of UK Patent Application No. 2016659.1, filed October 20, 2020, and UK Patent Application No. 2101665.4, filed February 5, 2021, both of which applications are incorporated herein by reference in their entirety.

BACKGROUND OF THE INVENTION

[0002] Cellular therapies hold great promise for combating previously intractable diseases. While the use of autologous cells is generally optimal, this approach can be cost-prohibitive and burdensome. Although allogeneic pluripotent stem cells (PSCs) provide greater scalability and cost savings, their utility is limited by the need to match human leukocyte antigen (HLA) class 1 alleles, the most genetically polymorphic region in the human genome. Mismatches in HLA class 1 haplotypes lead to the "self versus non-self" immune response that can result in the body's rejection of transplanted therapeutic cells. The general utility of recent efforts to engineer HLA complexes that are blocked from triggering a T-cell-activated immune response has been limited by the failure of these complexes to successfully engage the killer-cell immunoglobulin-like receptor (KIR), resulting in a "missing self" immune response. Consequently, there remains an unmet need for the development of engineered pluripotent stem cells that circumvent both T-cell- and KIR-mediated immune responses.

SUMMARY OF THE INVENTION

[0003] Provided herein, in an aspect, is a complex comprising one or more human leukocyte antigens (HLAs), wherein the one or more HLAs are inhibited from eliciting a T-cell response when the complex is interrogated by one or more T-cells.

[0003a] In one aspect, provided herein is a complex comprising: a segment comprising a peptide, one or more linkers, and a segment comprising a human HLA class 1 heavy chain sequence, wherein said human HLA class 1 heavy chain sequence comprises HLA-C, and wherein said one or more linkers comprises a conformation configured to not block one or more killer-cell immunoglobulin-like receptor binding sites on said human HLA class 1 heavy chain sequence; and wherein said human HLA class 1 heavy chain sequence comprises one or more mutations as compared to an endogenous HLA of the same type, wherein said mutations occur at one or more of amino acid residues 115, 122, 128, 194, 197, 198, 212, 214, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 243, 245, 248, 262, or any combination thereof.

[0003b] In another aspect, provided herein is a nucleic acid molecule encoding the complex described herein.

[0003c] In another aspect, provided herein is an engineered vector comprising the nucleic acid molecule described herein.

[0003d] In another aspect, provided herein is an isolated cell comprising said nucleic acid molecule described herein, or said vector described herein.

[0003e] In another aspect, provided herein is a method of generating an immune incompetent cell, comprising administering the complex described herein, or the nucleic acid molecule described herein, or the vector described herein, to a cell.

[0003f] In another aspect, provided herein is a therapeutically effective amount of said nucleic acid molecule described herein or said isolated cell described herein, for use in treating a disease or disorder in a subject in need thereof.

[0004] In some embodiments, the complex comprises, in N-terminus to C-terminus order, a segment comprising a peptide and a segment comprising a human HLA class 1 heavy chain sequence. In some embodiments, the peptide does not elicit a T-cell response when the peptide is interrogated by one or more T-cells. In some embodiments, the peptide is incapable of activating the one or more T-cells. In some embodiments, the peptide is capable of binding to a receptor of the one or more T-cells, and the binding is insufficient to activate the one or more T-cells. In some embodiments, the peptide binds to one or more HLA binding groove domain residues of the human HLA class 1 heavy chain sequence. In some embodiments, the peptide modulates a conformation of the human HLA class 1 heavy chain sequence. In some embodiments, the conformation prevents the one or more T-cells from binding to the human HLA class 1 heavy chain sequence. In some embodiments, the peptide comprises greater than or