Another immunotherapy approach is adoptive transfer of genetically engineered T cells expressing a transgenic T cell receptor (TCR) or a chimeric antigen receptor (CAR) directed against a tumor-associated antigen (TAA)[11,12]. This approach is particularly suitable for malignancies with low mutation burden that fail to induce endogenous T cell responses against TAAs. CAR T cells recognizing the CD19 antigen have demonstrated remarkable efficacy in relapsed and refractory B cell malignancies. However, these studies also suggested that the therapeutic effect was less evident in nodal disease with respect to bone marrow (BM) disease or leukemia, suggesting that an immunosuppressive microenvironment represents a major impediment towards successful immunotherapy, especially in solid tumor masses. Moreover, in fast-growing tumors such as B cell acute lymphoblastic leukemia (B-ALL), antigen loss occurs in up to 20% of patients treated with CD19 CAR T cells, illustrating a limitation of immunotherapy directed against a single antigen[11,13]. However, there is little data available on whether leukemia induces TAA-specific T cell responses outside of allogeneic transplant setting, and whether such a response can be potentiated for therapeutic purposes.

There remains a need for improved cancer therapies. The present invention achieves this need by establishing that improved efficacy can be achieved when a cytokine such as IFNα delivered by gene therapy is used in combination with other immunotherapeutic strategies.

SUMMARY

The inventors have surprisingly found that a cytokine such as an interferon delivered by gene therapy can boost the induction, consolidation and maintenance of anti-tumor responses and synergize with other immunotherapeutic strategies, in particular treatment with immune checkpoint inhibitors and treatment with tumor associated antigen (TAA)-specific T-cells.

In one aspect, there is provided the use of a hematopoietic stem cell (HSC), a hematopoietic progenitor cell (HPC), a myeloid/monocyte-committed progenitor cell, a macrophage or a monocyte comprising a vector wherein the vector comprises at least one mir-130a and/or mir-126 target sequence operably linked to a nucleotide sequence encoding a cytokine in the manufacture of a medicament for treating or preventing a cancer in a patient, wherein the medicament is to be administered in combination with an immune checkpoint inhibitor, a tumor associated antigen (TAA)-specific T-cell and/or 1-methyl-tryptophan (1-MT), preferably wherein the cytokine is an interferon (IFN), IL-12 or granulocyte-macrophage colony-

interferon (IFN), IL-12 or granulocyte-macrophage colony-stimulating factor (GM-CSF), preferably wherein the IFN is a type I IFN (preferably IFNα or IFNβ), or a type II IFN (preferably IFNγ), more preferably wherein the type I IFN is IFNα.

In yet another aspect, there is also provided the use of a hematopoietic stem cell (HSC), a hematopoietic progenitor cell (HPC), a myeloid/monocyte-committed progenitor cell, a macrophage or a monocyte comprising a vector wherein the vector comprises at least one mir-130a and/or mir-126 target sequence operably linked to a nucleotide sequence encoding a cytokine in the manufacture of a medicament for treating or preventing a cancer in a patient in need thereof, wherein the use comprises that the medicament is to be administered to the patient in combination with an immune checkpoint inhibitor, a tumor associated antigen (TAA)-specific T-cell and/or 1-methyl-tryptophan (1-MT), preferably wherein the TAA-specific T-cell expresses a chimeric antigen receptor (CAR) and/or a transgenic T-cell receptor (TCR), preferably wherein the cytokine is an interferon (IFN), IL-12 or granulocyte-macrophage colony-stimulating factor (GM-CSF), preferably wherein the IFN is a type I IFN (preferably IFNα or IFNβ), or a type II IFN (preferably IFNγ), more preferably wherein the type I IFN is IFNα.

In yet another aspect, there is also provided the use of a tumor associated antigen (TAA)-specific T-cell, an immune checkpoint inhibitor, and/or 1-methyl-tryptophan (1-MT) in the manufacture of a medicament for treating or preventing a cancer in a patient previously administered with a hematopoietic stem cell (HSC), a hematopoietic progenitor cell (HPC), a myeloid/monocyte-committed progenitor cell, a macrophage or a monocyte comprising a vector wherein the vector comprises at least one mir-130a and/or mir-126 target sequence operably linked to a nucleotide sequence encoding a cytokine, which comprises the step that the medicament is to be administered to the patient, preferably wherein the TAA-specific T-cell expresses a chimeric antigen receptor (CAR) and/or a transgenic T-cell receptor (TCR), preferably wherein the cytokine is an interferon (IFN), IL-12 or granulocyte-macrophage colony-stimulating factor (GM-CSF), preferably wherein the IFN is a type I IFN (preferably IFNα or IFNβ), or a type II IFN (preferably IFNγ), more preferably wherein the type I IFN is IFNα.

In a further aspect, the present disclosure refers to the use of a hematopoietic stem cell (HSC), a hematopoietic progenitor cell (HPC), a myeloid/monocyte-committed progenitor cell, a macrophage or a monocyte comprising a vector comprising at least one mir-130a and/or mir-126 target sequence operably linked to a nucleotide sequence encoding a first cytokine, and a vector comprising at least one mir-130a and/or mir-126 target sequence operably linked to a nucleotide sequence encoding a second cytokine in the manufacture of a medicament for treating or preventing a cancer in a patient, wherein the first and second

CLAIMS

1. Use of a hematopoietic stem cell (HSC), a hematopoietic progenitor cell (HPC), a myeloid/monocyte-committed progenitor cell, a macrophage or a monocyte comprising a vector wherein the vector comprises at least one mir-130a and/or mir-126 target sequence operably linked to a nucleotide sequence encoding a cytokine in the manufacture of a medicament for treating or preventing a cancer in a patient, wherein the medicament is to be administered in combination with an immune checkpoint inhibitor, a tumor associated antigen (TAA)-specific T-cell and/or 1-methyl-tryptophan (1-MT),

preferably wherein the cytokine is an interferon (IFN), IL-12 or granulocyte-macrophage colony-stimulating factor (GM-CSF),

preferably wherein the IFN is a type I IFN (preferably IFNα or IFNβ), or a type II IFN (preferably IFNγ),

more preferably wherein the type I IFN is IFNα.

2. The use according to claim 1, wherein the medicament is to be used in combination with an immune checkpoint inhibitor and a TAA-specific T-cell.

3. The use according to claim 1 or 2, wherein the TAA-specific T-cell expresses a chimeric antigen receptor (CAR) and/or a transgenic T cell receptor (TCR)

4. The use according any preceding claim, wherein the TAA is selected from the group consisting of carcinoembryonic antigen (CEA), estrogen receptor, progesterone receptor, ephrinB2, ROR1, mesothelin, c-Met, GD-2, and MAGE A3 TCR, 4-1BB, adenocarcinoma antigen, alpha-fetoprotein, BAFF, B-lymphoma cell, C242 antigen, carbonic anhydrase 9 (CA-IX), CCR4, CD152, CD200, CD22, CD19, CD22, CD123, CD221, CD23 (IgE receptor), CD28, CD4, CD40, CD44, CD44 v6, CD51, CD52, CD56, CD74, CD80, CS-1, CNT0888, CTLA-4, DR5, EpCAM, CD3, fibronectin extra domain-B, folate receptor 1, glycoprotein 75, GPNMB, HGF, human scatter factor receptor kinase, IGF-1 receptor, IGF-I, IgGl, L1-CAM, IL-13, IL-6, insulin-like growth factor I receptor, integrin α5β1, integrin αvβ3, MORAb-009, MS4A1, mucin CanAg, N-glycolylneuraminic acid, NPC-1C, PDGF-Rα, PDL192, phosphatidylserine, prostatic carcinoma cells, RANKL, RON, SCH 900105, SDC1, SLAMF7, tenascin C, TGF beta 2, TGF-β, TRAIL-R1, TRAIL-R2, tumor antigen CTAA16.88, Vascular endothelial growth, factor (VEGF), VEGF-A, VEGFR-1, VEGFR2, vimentin, 5T4, CD5, CD19, CD20, CD21, CD25, CD37, CD30, CD33, CD45, CAMPATH-1 (CDw52), HLA-DR,

Anti-idiotype, TAG-72, Ep-CAM, MUC1, Folate-binding protein, A33, G250, Prostate-specific membrane antigen, (PSMA), Prostate specific antigen (PSA), Ferritin, Gangliosides (e.g. GD2, GD3, GM2), Le^y, CA-125, CA19-9, Epidermal growth factor receptor (EGFR), p185HER2, IL-2 receptor, de2-7 EGFR, Fibroblast activation protein (FAP), Tenascin, metalloproteinases, Endosialin, Carbonic anhydrase, Galectin 9, Aldolase A, eIFγ4, Tyrosinase, Galectin 4, HERKV-K10, p53, NY-LU-12, Restin, NY-CO-38, MAGE-1, MAGE-4a, SSX2, NY-ESO-1, SCP-1, 707-AP, AFP, ART-4, BAGE, b-catenin/m, Bcr-abl, CAMEL, CAP-1, CASP-8, CDC27m, CDK4/m, CT, Cyp-B, DAM-6 (MAGE-B2) and DAM-10 (MAGE-B1), ELF2M, ETV6-AML1, G250, GAGE, GnT-V, Gp100, HAGE, HER-2/neu, HLA-A*0201-R170I, HPV-E7, HSP70-2M, HST-2, hTERT (hTRT), iCE, KIAA0205, LAGE, LDLR/FUT, MAGE, MART-1/Melan-A, MC1R, Myosin/m, MUC1, MUM-1, MUM-2, MUM-3, NA88-A, NY-ESO-1, P15, p190 minor bcr-abl, Pml/RARa, PRAME, RAGE, RU1, RU2, SAGE, SART-1, SART-3, TEL/AML1, TPI/m, TRP-1, protein 1, gp75, TRP-2, TRP-2/INT2 and WT1,

preferably, wherein the TAA-specific T-cell expresses a CD19-specific CAR.

5. The use according to any preceding claim, wherein the TAA-specific T-cell is derived from a cell isolated from the patient.

6. The use according to any preceding claim, wherein the TAA-specific T-cell has been engineered to disrupt at least one endogenous gene, preferably wherein the at least one endogenous gene is selected from an endogenous gene encoding a TCR α chain, a TCR β chain and a major histocompatibility complex (MHC).

7. The use according to any preceding claim, wherein the immune checkpoint inhibitor:

(i) is an antibody, preferably wherein the immune checkpoint inhibitor antibody is selected from the group consisting of an anti-CTLA4 antibody, an anti-PD1 antibody, an anti-PDL1 antibody, an anti-PDL2 antibody and an anti-LAG-3 antibody; and/or

(ii) inhibits an inhibitory checkpoint molecule selected from the group consisting of A2AR (Adenosine A2A receptor), B7-H3 (CD276), B7-H4 (VTCN1), BTLA (B and T Lymphocyte Attenuator; CD272), HVEM (Herpesvirus Entry Mediator), CTLA-4 (Cytotoxic T-Lymphocyte-Associated protein 4; CD152), IDO (Indoleamine 2,3-dioxygenase), TDO (tryptophan 2,3-dioxygenase), KIR (Killer-cell Immunoglobulin-like Receptor), LAG3 (Lymphocyte Activation Gene-3), PD-1 (Programmed Death 1 receptor), PD-L1 (PD-1 ligand 1), PD-L2 (PD-1 ligand 2), TIM-3 (T-cell Immunoglobulin domain and Mucin domain 3), VISTA (V-domain Ig Suppressor of T cell Activation), B7-1 (CD80), and B7-2 (CD86).

8. The use according to any preceding claim, wherein the vector comprises at least one mir-130a target sequence and at least one mir-126 target sequence, preferably wherein the vector comprises two mir-130a target sequences and two mir-126 target sequences.

9. The use according to any preceding claim, wherein the vector further comprises a tissue specific promoter operably linked to the nucleotide sequence encoding the cytokine, preferably wherein the tissue specific promoter is a TEK (Tie2) promoter.

10. The use according to any preceding claim, wherein the cancer is a hematological malignancy or a solid tumor, preferably wherein the hematological malignancy is selected from the group consisting of acute myeloid leukemia (AML), lymphoblastic leukemia, acute lymphoblastic leukemia (ALL), myelodysplastic syndromes (MDS), myeloproliferative neoplasms (MPN), primary myelofibrosis, essential thrombocythemia, polycythemia vera, atypical chronic myeloid leukemia, chronic myeloid leukemia (CML), lymphoma, multiple myeloma, non Hodgkin lymphoma and Hodgkin lymphoma; or preferably wherein the solid tumor is selected from the group consisting of lung cancer, breast cancer, oesophageal cancer, gastric cancer, colon cancer, cholangiocarcinoma, pancreatic cancer, ovarian cancer, head and neck cancers, synovial sarcoma, angiosarcoma, osteosarcoma, thyroid cancer, endometrial cancer, neuroblastoma, rabdomyosarcoma, liver cancer, melanoma, prostate cancer, renal cancer, soft tissue sarcoma, urothelial cancer, biliary cancer, glioblastoma, cervical cancer and colorectal cancer.

11. Use of a tumor associated antigen (TAA)-specific T-cell in the manufacture of a medicament for treating or preventing a cancer in a patient wherein the patient has previously been administered with a hematopoietic stem cell (HSC) a hematopoietic progenitor cell (HPC), a myeloid/monocyte-committed progenitor cell, a macrophage or a monocyte comprising a vector wherein the vector comprises at least one mir-130a and/or mir-126 target sequence operably linked to a nucleotide sequence encoding a cytokine, preferably wherein the TAA is selected from the group consisting of carcinoembryonic antigen (CEA), estrogen receptor, progesterone receptor, ephrinB2, ROR1, mesothelin, c-Met, GD-2, and MAGE A3 TCR, 4-1BB, adenocarcinoma antigen, alpha-fetoprotein, BAFF, B-lymphoma cell, C242 antigen, carbonic anhydrase 9 (CA-IX), CCR4, CD152, CD200, CD22, CD19, CD22, CD123, CD221, CD23 (IgE receptor), CD28, CD4, CD40, CD44, CD44 v6, CD51, CD52, CD56, CD74, CD80, CS-1, CNT0888, CTLA-4, DR5, EpCAM, CD3, fibronectin extra domain-B, folate receptor 1, glycoprotein 75, GPNMB, HGF, human scatter factor receptor kinase, IGF-1 receptor, IGF-I, IgGl, L1-CAM, IL-13, IL-6, insulin-like growth factor I receptor, integrin α5β1, integrin αvβ3, MORAb-009, MS4A1, mucin CanAg, N-glycolylneuraminic acid, NPC-1C, PDGF-Rα, PDL192, phosphatidylserine, prostatic

carcinoma cells, RANKL, RON, SCH 900105, SDC1, SLAMF7, tenascin C, TGF beta 2, TGF-β, TRAIL-R1, TRAIL-R2, tumor antigen CTAA16.88, Vascular endothelial growth, factor (VEGF), VEGF-A, VEGFR-1, VEGFR2, vimentin, 5T4, CD5, CD19, CD20, CD21, CD25, CD37, CD30, CD33, CD45, CAMPATH-1 (CDw52), HLA-DR, Anti-idiotype, TAG-72, Ep-CAM, MUC1, Folate-binding protein, A33, G250, Prostate-specific membrane antigen, (PSMA), Prostate specific antigen (PSA), Ferritin, Gangliosides (e.g. GD2, GD3, GM2), Le^y, CA-125, CA19-9, Epidermal growth factor receptor (EGFR), p185HER2, IL-2 receptor, de2-7 EGFR, Fibroblast activation protein (FAP), Tenascin, metalloproteinases, Endosialin, Carbonic anhydrase, Galectin 9, Aldolase A, eIFγ4, Tyrosinase, Galectin 4, HERKV-K10, p53, NY-LU-12, Restin, NY-CO-38, MAGE-1, MAGE-4a, SSX2, NY-ESO-1, SCP-1, 707-AP, AFP, ART-4, BAGE, b-catenin/m, Bcr-abl, CAMEL, CAP-1, CASP-8, CDC27m, CDK4/m, CT, Cyp-B, DAM-6 (MAGE-B2) and DAM-10 (MAGE-B1), ELF2M, ETV6-AML1, G250, GAGE, GnT-V, Gp100, HAGE, HER-2/neu, HLA-A*0201-R170I, HPV-E7, HSP70-2M, HST-2, hTERT (hTRT), iCE, KIAA0205, LAGE, LDLR/FUT, MAGE, MART-1/Melan-A, MC1R, Myosin/m, MUC1, MUM-1, MUM-2, MUM-3, NA88-A, NY-ESO-1, P15, p190 minor bcr-abl, Pml/RARa, PRAME, RAGE, RU1, RU2, SAGE, SART-1, SART-3, TEL/AML1, TPI/m, TRP-1, protein 1, gp75, TRP-2, TRP-2/INT2 and WT1, preferably wherein the TAA-specific T-cell expresses a chimeric antigen receptor (CAR) and/or a transgenic T-cell receptor (TCR),

preferably wherein the cytokine is an interferon (IFN), IL-12 or granulocyte-macrophage colony-stimulating factor (GM-CSF),

preferably wherein the IFN is a type I IFN (preferably IFNα or IFNβ), or a type II IFN (preferably IFNγ),

more preferably wherein the type I IFN is IFNα,

preferably, wherein the TAA-specific T-cell expresses a CD19-specific CAR.

12. Use of an immune checkpoint inhibitor in the manufacture of a medicament for treating or preventing a cancer in a patient wherein the patient has previously been administered with a hematopoietic stem cell (HSC), a hematopoietic progenitor cell (HPC), a myeloid/monocyte-committed progenitor cell, a macrophage or a monocyte comprising a vector wherein the vector comprises at least one mir-130a and/or mir-126 target sequence operably linked to a nucleotide sequence encoding a cytokine, preferably wherein the immune checkpoint inhibitor is an antibody, more preferably wherein the immune checkpoint inhibitor antibody is selected from the group consisting of an anti-CTLA4 antibody, an anti-PD1 antibody, an anti-PDL1 antibody, an anti-PDL2 antibody and an anti-LAG-3 antibody,

preferably wherein the cytokine is an interferon (IFN), IL-12 or granulocyte-macrophage colony-stimulating factor (GM-CSF),

preferably wherein the IFN is a type I IFN (preferably IFNα or IFNβ), or a type II IFN (preferably IFNγ),

more preferably wherein the type I IFN is IFNα.

13. Use of 1-methyl-tryptophan (1-MT) in the manufacture of a medicament for treating or preventing a cancer in a patient wherein the patient has previously been administered with a hematopoietic stem cell (HSC), a hematopoietic progenitor cell (HPC), a myeloid/monocyte-committed progenitor cell, a macrophage or a monocyte comprising a vector wherein the vector comprises at least one mir-130a and/or mir-126 target sequence operably linked to a nucleotide sequence encoding a cytokine,

preferably wherein the cytokine is an interferon (IFN), IL-12 or granulocyte-macrophage colony-stimulating factor (GM-CSF),

preferably wherein the IFN is a type II IFN (preferably IFNγ).

14. Use of a combination of an immune checkpoint inhibitor and a tumor associated antigen (TAA)-specific T-cell in the manufacture of a medicament for treating or preventing a cancer in a patient wherein the patient has previously been administered with a hematopoietic stem cell (HSC) or a hematopoietic progenitor cell (HPC) comprising a vector wherein the vector comprises at least one mir-130a and/or mir-126 target sequence operably linked to a nucleotide sequence encoding a cytokine, preferably wherein the TAA-specific T-cell expresses a chimeric antigen receptor (CAR) and/or a transgenic T-cell receptor (TCR),

preferably wherein the cytokine is an interferon (IFN), IL-12 or granulocyte-macrophage colony-stimulating factor (GM-CSF),

preferably wherein the IFN is a type I IFN (preferably IFNα or IFNβ), or a type II IFN (preferably IFNγ),

more preferably wherein the type I IFN is IFNα.

15. The use according to any one of claims 11-14, wherein the vector comprises at least one mir-130a target sequence and at least one mir-126 target sequence, preferably wherein the vector comprises two mir-130a target sequences and two mir-126 target sequences.

16. The use according to any one of claims 11-15, wherein the vector further comprises a tissue specific promoter operably linked to the nucleotide sequence encoding the cytokine, preferably wherein the tissue specific promoter is a TEK (Tie2) promoter.

17. The use according to any one of claims 11-16, wherein the cancer is a hematological malignancy or a solid tumor, preferably wherein the hematological malignancy is selected from the group consisting of acute myeloid leukemia (AML), lymphoblastic leukemia, acute lymphoblastic leukemia (ALL), myelodisplastic syndromes, lymphoma, multiple myeloma, non Hodgkin lymphoma and Hodgkin lymphoma; or preferably wherein the solid tumor is selected from the group consisting of lung cancer, breast cancer, oesophageal cancer, gastric cancer, colon cancer, cholangiocarcinoma, pancreatic cancer, ovarian cancer, head and neck cancers, synovial sarcoma, angiosarcoma, osteosarcoma, thyroid cancer, endometrial cancer, neuroblastoma, rabdomyosarcoma, liver cancer, melanoma, prostate cancer, renal cancer, soft tissue sarcoma, urothelial cancer, biliary cancer, glioblastoma, cervical cancer and colorectal cancer.

18. Use of a hematopoietic stem cell (HSC), a hematopoietic progenitor cell (HPC), a myeloid/monocyte-committed progenitor cell, a macrophage or a monocyte comprising a vector wherein the vector comprises at least one mir-130a and/or mir-126 target sequence operably linked to a nucleotide sequence encoding a cytokine in the manufacture of a medicament for treating or preventing a cancer in a patient in need thereof, wherein the use comprises that the medicament is to be administered to the patient in combination with an immune checkpoint inhibitor, a tumor associated antigen (TAA)-specific T-cell and/or 1-methyl-tryptophan (1-MT), preferably wherein the TAA-specific T-cell expresses a chimeric antigen receptor (CAR) and/or a transgenic T-cell receptor (TCR),

preferably wherein the cytokine is an interferon (IFN), IL-12 or granulocyte-macrophage colony-stimulating factor (GM-CSF),

preferably wherein the IFN is a type I IFN (preferably IFNα or IFNβ), or a type II IFN (preferably IFNγ),

more preferably wherein the type I IFN is IFNα.

19. Use of a tumor associated antigen (TAA)-specific T-cell, an immune checkpoint inhibitor, and/or 1-methyl-tryptophan (1-MT) in the manufacture of a medicament for treating or preventing a cancer in a patient previously administered with a hematopoietic stem cell (HSC), a hematopoietic progenitor cell (HPC), a myeloid/monocyte-committed progenitor cell, a macrophage or a monocyte comprising a vector wherein the vector comprises at least

one mir-130a and/or mir-126 target sequence operably linked to a nucleotide sequence encoding a cytokine, which comprises the step that the medicament is to be administered to the patient, preferably wherein the TAA-specific T-cell expresses a chimeric antigen receptor (CAR) and/or a transgenic T-cell receptor (TCR),

preferably wherein the cytokine is an interferon (IFN), IL-12 or granulocyte-macrophage colony-stimulating factor (GM-CSF),

preferably wherein the IFN is a type I IFN (preferably IFNα or IFNβ), or a type II IFN (preferably IFNγ),

more preferably wherein the type I IFN is IFNα.