[04] In one example, disclosed herein is a method of inhibiting or reducing the incidence or the severity of immunotherapy-related toxicity in a subject, the method comprising a step of administering a recombinant GM-CSF antagonist to the subject.

[04a] In one aspect, disclosed herein is a use of a recombinant hGM-CSF antagonist in the manufacture of a medicament for inhibiting or reducing the incidence or the severity of immunotherapy-related toxicity in a subject, wherein the recombinant hGM-CSF antagonist comprises an anti-hGM-CSF antibody comprising a variable heavy chain (VH) region comprising a CDRl comprising the amino acid sequence of SEQ ID NO: 25, a CDR2 comprising the amino acid sequence of SEQ ID NO: 27 and a CDR3 comprising the amino acid sequence SEQ ID NO: 15; and a variable light chain (VL) region comprising a CDRl comprising the amino acid sequence of SEQ ID NO: 31, a CDR2 comprising the amino acid sequence of SEQ ID NO: 33 and a CDR3 comprising the amino acid sequence SEQ ID NO: 18, wherein the administration of the medicament inhibits or reduces the incidence or the severity of immunotherapy-related toxicity in said subject.

[05] In a related example, said immunotherapy comprises adoptive cell transfer, administration of monoclonal antibodies, administration of cytokines, administration of a cancer vaccine, T cell engaging therapies, or any combination thereof.

[06] In another example, adoptive cell transfer comprises administering chimeric antigen receptor-expressing T-cells (CAR T-cells), T-cell receptor (TCR) modified T-cells, tumor-infiltrating lymphocytes (TIL), chimeric antigen receptor (CAR)-modified natural killer cells, or dendritic cells, or any combination thereof. In a related example, the monoclonal antibody is selected from a group comprising: anti-CD3, anti-CD52, anti-PD1, anti-PD-L1, anti-CTLA4, anti-CD20, anti-BCMA antibodies, bi-specific antibodies, or bispecific T-cell engager (BiTE) antibodies, or any combination thereof. In a related example, the cytokines are selected from a group comprising: IFNα, IFNβ, IFNγ, IFNλ, IL-1, IL-2, IL-6, IL-7, IL-15, IL-21, IL-11, IL-12, IL-18, GM-CSF, TNFα, or any combination thereof.

[07] In another example, inhibiting or reducing the incidence or the severity of immunotherapy-related toxicity comprises reducing the concentration of at least one inflammation-associated factor in the serum, tissue fluid, or in the CSF of the subject. In a related example, the inflammation-associated factor is selected from a group comprising:

C-reactive protein, GM-CSF, IL-1, IL-2, sIL2Rα, IL-5, IL-6, IL-8, IL-10, IP10, IL-15, MCP-1 (AKA CCL2), MIG, MIP1β, IFNγ, CX3CR1, or TNFα, or any combination thereof. In another example, the administration of recombinant GM-CSF antagonist does not reduce the efficacy of said immunotherapy. In another example, the administration of recombinant GM-CSF antagonist increases the efficacy of said immunotherapy. In another example, administration of recombinant GM-CSF antagonist occurs prior to, concurrent

cell function, synergy with a checkpoint inhibitor, or any combination thereof. In another example, said increased CAR-T cell expansion comprises at least a 50% increase compared to a control. In another example, said increased CAR-T cell expansion comprises at least a one quarter log expansion compared to a control. In another example, said increased cell expansion comprises at least a one- half log expansion compared to a control. In another example, said increased cell expansion comprises at least a one log expansion compared to a control. In another example, said increased cell expansion comprises a greater than one log expansion compared to a control.

[019] In an example, the GM-CSF antagonist comprises a neutralizing antibody. In another example, the neutralizing antibody is a monoclonal antibody.

[020] In an example, disclosed herein is a method of inhibiting or reducing the incidence or the severity of CAR-T related toxicity in a subject, the method comprising a step of administering a recombinant GM-CSF antagonist to the subject, wherein said administering inhibits or reduces the incidence or the severity of CAR-T related toxicity in said subject. In an example, said CAR-T related toxicity comprises neurotoxicity, CRS, or a combination thereof. In some examples, the CAR-T cell related neurotoxicity is reduced by about 50% compared to a reduction in neurotoxicity in a subject treated with CAR-T cells and a control antibody. In various examples, the recombinant GM-CSF antagonist is a GM-CSF neutralizing antibody in accordance with examples described herein.

[020a] In another aspect, disclosed herein is a use of a recombinant hGM-CSF antagonist in the manufacture of a medicament for inhibiting or reducing the incidence or the severity of CAR-T related toxicity in a subject, wherein administration of the medicament inhibits or reduces the incidence or the severity of CAR-T related toxicity in said subject.

[021] In another example, said inhibiting or reducing incidence of CRS comprises increasing survival time and/or time to relapse, reducing macrophage activation, reducing T cell activation, or reducing the concentration of circulating GM-CSF, or any combination thereof. In another example, said subject presents with fever (with or without rigors,

[024] In one example, the subject is a human.

[025] In one example, disclosed herein is a GM-CSF antagonist for use in a method of inhibiting or reducing the incidence or severity of immunotherapy-related toxicity in a subject, the method comprising a step of administering a recombinant GM-CSF antagonist to the subject. In one example, disclosed herein is a pharmaceutical composition comprising an anti-GM-CSF antagonist.

## BRIEF DESCRIPTION OF THE DRAWINGS

[026] **Figure 1** Provides exemplary $V_H$ and $V_L$ sequences of anti-GM-CSF antibodies.

[027] **Figures 2A-2B** Binding of GM-CSF to Ab1 (Figure 2A) or Ab2 (Figure 2B) determined by surface plasmon resonance analysis at 37°C (Biacore 3000). Ab1 and Ab2 were captured on anti Fab polyclonal antibodies immobilized on the Biacore chip. Different concentrations of GM-CSF were injected over the surface as indicated. Global fit analysis was carried out assuming a 1:1 interaction using Scrubber2 software.

[028] **Figures 3A-3B** Binding of Ab1 and Ab2 to glycosylated (Figure 3A) and non-glycosylated GM-CSF (Figure 3B). Binding to glycosylated GM-CSF expressed from human 293 cells or non-glycosylated GM-CSF expressed in *E. coli* was determined by ELISA. Representative results from a single experiment are shown (exp 1). Two-fold dilutions of Ab1 and Ab2 starting from 1500ng/ml were applied to GM-CSF coated wells. Each point represents mean $\pm$ standard error for triplicate determinations. Sigmoidal curve fit was performed using Prism 5.0 Software (Graphpad).

[029] **Figures 4A-4B** Competition ELISA demonstrating binding of Ab1 and Ab2 to a shared epitope. ELISA plates coated with 50 ng/well of recombinant GM-CSF were incubated with various concentrations of antibody (Ab2, Ab1 or isotype control antibody

**WHAT IS CLAIMED IS:**

1. Use of a recombinant hGM-CSF antagonist in the manufacture of a medicament for inhibiting or reducing the incidence or the severity of immunotherapy-related toxicity in a subject, wherein the recombinant hGM-CSF antagonist comprises an anti-hGM-CSF antibody comprising a variable heavy chain (VH) region comprising a CDRl comprising the amino acid sequence of SEQ ID NO: 25, a CDR2 comprising the amino acid sequence of SEQ ID NO: 27 and a CDR3 comprising the amino acid sequence SEQ ID NO: 15; and a variable light chain (VL) region comprising a CDRl comprising the amino acid sequence of SEQ ID NO: 31, a CDR2 comprising the amino acid sequence of SEQ ID NO: 33 and a CDR3 comprising the amino acid sequence SEQ ID NO: 18, wherein the administration of the medicament inhibits or reduces the incidence or the severity of immunotherapy-related toxicity in said subject.

2. The use of claim 1, wherein said immunotherapy comprises adoptive cell transfer, administration of monoclonal antibodies, administration of cytokines, administration of a cancer vaccine, T cell engaging therapies, or any combination thereof.

3. The use of claim 2, wherein said adoptive cell transfer comprises administering chimeric antigen receptor-expressing T-cells (CAR T-cells), T-cell receptor (TCR) modified T-cells, tumor-infiltrating lymphocytes (TIL), chimeric antigen receptor (CAR)-modified natural killer cells, or dendritic cells, or any combination thereof.

4. The use of claim 2, wherein said monoclonal antibody is selected from a group comprising: anti-CD3, anti-CD52, anti-PD1, anti-PD-L1, anti-CTLA4, anti-CD20, anti-BCMA antibodies, bi-specific antibodies, or bispecific T-cell engager (BiTE) antibodies, or any combination thereof.

5. The use of claim 2, wherein said cytokines are selected from a group comprising: IFNα, IFNβ, IFNγ, IFNλ, IL-2, IL-7, IL-15, IL-21, IL-11, IL-12, IL-18, hGM-CSF, TNFα, or any combination thereof.

6. The use of any of claims 1-5, wherein said inhibiting or reducing the incidence or the severity of immunotherapy-related toxicity comprises reducing the concentration of at

least one inflammation-associated factor in ~~the~~ serum, tissue fluid, or in ~~the~~ cerebrospinal fluid (CSF) of said subject.

7. The use of claim 6, wherein said inflammation-associated factor is selected from a group comprising: C-reactive protein, hGM-CSF, IL-2, sIL2Rα, IL-5, IL-6, IL-8, IP10, IL-10, IL-15, MCP-1, MIG, MIP1β, IFNγ, CX3CR1, or TNFα, or any combination thereof.

8. The use of any of claims 1-7, wherein administration of said medicament does not reduce the efficacy of said immunotherapy.

9. The use of any of claims 1-8, wherein said immunotherapy is to be administered at higher doses than it would be administered without the administration of said medicament.

10. The use of any of claims 1-9, wherein administration of said medicament is to occur prior to, concurrent with, or following said immunotherapy.

11. The use of any of claims 1-10, wherein said medicament is to be co-administered with corticosteroids, anti-IL-6 antibodies, tocilizumab, cyclosporine, antiepileptics, benzodiazepines, acetazolamide, hyperventilation therapy, or hyperosmolar therapy, or any combination thereof.

12. The use of any of claims 1-11, wherein said immunotherapy-related toxicity comprises a brain disease, damage or malfunction.

13. The use of claim 12, wherein said brain disease, damage or malfunction comprises CAR-T cell related neurotoxicity or CAR-T cell related encephalopathy syndrome (CRES).

14. The use of claim 13, wherein the CAR-T cell related neurotoxicity is reduced by about 90% compared to a reduction in neurotoxicity in a subject treated with CAR-T cells.

15. The use of any of claims 12-14, wherein said inhibiting or reducing incidence of a brain disease, damage or malfunction comprises reducing headaches, delirium, anxiety, tremor, seizure activity, confusion, alterations in wakefulness, hallucinations, dysphasia, ataxia, apraxia, facial nerve palsy, motor weakness, seizures, nonconvulsive EEG seizures, altered levels of consciousness, coma, endothelial activation, vascular leak, intravascular coagulation, or any combination thereof in said subject.

16. The use of any of claims 12-15, wherein serum concentration of ANG2 or VWF, or serum ANG2:ANG1 ratio of said subject is reduced.

17. The use of any of claims 12-16, wherein said subject has a body temperature above 38°C, IL6 serum concentration above 16 pg/ml, or MCP-1 serum concentration above 1,300 pg/ml during the first 36 hours after infusion of said CAR-T cells.

18. The use of any of claims 12-17, wherein said subject is predisposed to have said brain disease, damage or malfunction.

19. The use of any of claims 12-18, wherein said subject has an ANG2:ANG1 ratio in serum above 1 prior to the infusion of said CAR-T cells.

20. The use of any of claims 1-11, wherein said immunotherapy-related toxicity comprises hemophagocytic lymphohistiocytosis (HLH) or macrophage-activation syndrome (MAS).

21. The use of claim 20, wherein said inhibiting or reducing incidence of HLH or MAS comprises increasing survival time and/or time to relapse, reducing macrophage activation, reducing T cell activation, reducing the concentration of circulating IFNγ, or reducing the concentration of circulating of hGM-CSF, or any combination thereof.

22. The use of any of claims 20 or 21, wherein said subject presents with fever, splenomegaly, cytopenias involving two or more lines, hypertriglyceridemia, hypofibrinogenemia, hemophagocytosis, low or absent NK-cell activity, ferritin serum concentration above 500 U/ml, or soluble CD25 serum concentration above 2400 U/ml, or any combination thereof.

23. The use of any of claims 20-22, wherein said subject is predisposed to acquiring HLH or MAS.

24. The use of any of claims 20-23, wherein said subject carries a mutation in a gene selected from: PRF1, UNC13D, STX11, STXBP2, or RAB27A, or has reduced expression of perforin, or any combination thereof.

25. The use of any one of claims 1-24, wherein the anti-hGM-CSF antibody blocks binding of hGM-CSF to the alpha subunit of the hGM-CSF receptor.

26. The use of any of claims 1-24, wherein the anti-hGM-CSF antibody is a monoclonal antibody.

27. The use of any of claims 25-26, wherein the anti-hGM-CSF antibody is a hGM-CSF neutralizing antibody.

28. The use of any of claims 25-27, wherein the anti-hGM-CSF antibody is a recombinant or chimeric antibody.

29. The use of any of claims 25-28, wherein the anti-hGM-CSF antibody is an engineered human antibody.

30. The use of any of claims 25-29, wherein the VH region CDR3 comprises RQRFPYYFDY (SEQ ID NO: 15).

31. The use of claim 30, wherein the VH region has the sequence of VH#5 comprising the amino acid sequence of SEQ ID NO:5.

32. The use of any of claims 25-31, wherein the anti-hGM-CSF antibody comprises a VL-region that comprises a CDR3 comprising the amino acid sequence FNK.

33. The use of claim 32, wherein the anti-hGM-CSF antibody comprises a VL region that comprises a CDR3 comprising QQFNKSPLT (SEQ ID NO: 18).

34. The use of claim 32, wherein the VL region has the sequence of VK#2 comprising the amino acid sequence of SEQ ID NO: 7.

35. The use of any of claims 25-29, wherein the anti-hGM-CSF antibody has a VH region CDR3 binding specificity determinant RQRFPY (SEQ ID NO: 12) and a VL region that has a CDR3 comprising QQFNKSPLT (SEQ ID NO: 18).

36. The use of any of claims 25-29, wherein the anti-hGM-CSF antibody has a VH region comprising the amino acid sequence of SEQ ID NO:5 and a VL region comprising the amino acid sequence of SEQ ID NO: 7.

37. The use of any of claims 25-36, wherein the VH region or the VL region, or both the VH and VL region amino acid sequences comprise a methionine at the N-terminus.

38. Use of a recombinant hGM-CSF antagonist in the manufacture of a medicament for inhibiting or reducing the incidence or the severity of CAR-T related toxicity in a subject,

wherein administration of the medicament inhibits or reduces the incidence or the severity of CAR-T related toxicity in said subject.

39. The use of claim 38, wherein said CAR-T related toxicity comprises neurotoxicity, Cytokine Release Syndrome (CRS), or a combination thereof.

40. The use of claim 39, wherein the CAR-T cell related neurotoxicity is reduced by about 50% compared to a reduction in neurotoxicity in a subject treated with CAR-T cells.

41. The use of claim 38-40, wherein the inhibiting or reducing the incidence or the severity of CAR-T related toxicity comprises increasing survival time and/or time to relapse, reducing macrophage activation, reducing T cell activation, or reducing the concentration of circulating hGM-CSF, or any combination thereof, wherein the inhibiting or reducing the incidence or the severity of CAR-T related toxicity comprises inhibiting or reducing incidence of Cytokine Release Syndrome (CRS).

42. The use of any of claims 38-40, wherein said subject presents with fever (with or without rigors, malaise, fatigue, anorexia, myalgia, arthralgia, nausea, vomiting, headache, skin rash, diarrhea, tachypnea, hypoxemia, hypoxia, shock, cardiovascular tachycardia, widened pulse pressure, hypotension, capillary leak, increased early cardiac output, diminished late cardiac output, elevated D-dimer, hypofibrinogenemia with or without bleeding, azotemia, transaminitis, hyperbilirubinemia, mental status changes, confusion, delirium, frank aphasia, hallucinations, tremor, dysmetria, altered gait, seizures, organ failure, or any combination thereof.

43. The use of any of claims 38-42, wherein the inhibiting or reducing the incidence or the severity of CAR-T related toxicity comprises preventing the onset of CAR-T related toxicity.

44. The use of any of claims 1-43, wherein the subject is a human.