METHODS OF TREATING IMMUNOTHERAPY-RELATED TOXICITY USING A GM-CSF ANTAGONIST

CROSS-REFERENCE TO RELATED APPLICATIONS

[01] This application claims priority to U.S. Provisional Application Nos. 62/567,187, filed October 2, 2017, and 62/729,043, filed September 10, 2018, which are hereby incorporated by reference.

FIELD OF THE DISCLOSURE

[02] The disclosure herein provides methods of inhibiting or reducing the incidence and/or the severity of immunotherapy-related toxicity in a subject, the method comprising administering a recombinant GM-CSF antagonist to the subject.

BACKGROUND

[03] Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a cytokine secreted by various cell types including macrophages, T cells, mast cells, natural killer cells, endothelial cells and fibroblasts. GM-CSF stimulates the differentiation of granulocytes and of monocytes. Monocytes, in turn, migrate into tissue and mature into macrophages and dendritic cells. Thus, secretion of GM-CSF leads to a rapid increase in macrophage numbers. GM-CSF is also involved in the inflammatory response in the Central Nervous System (CNS) causing influx of blood-derived monocytes and macrophages, and the activation of astrocytes and microglia. Immuno-related toxicities comprise potentially life-threatening immune responses that occur as a result of the high levels of immune activation occurring from different immunotherapies. Immuno-related toxicity is currently a major complication for the application of immunotherapies in cancer patients. It is clear that there remains a critical need for methods of preventing and treating immuno-related toxicity. An ideal method will minimize the risk of these life-threatening complications without affecting the efficacy of the immunotherapy and could potentially even improve the efficacy by allowing, for example, safe increased dosing of immunotherapeutic compounds and/or an expansion of T cells.

SUMMARY

[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 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

with, or following immunotherapy. In a related example, the recombinant GM-CSF antagonist is co-administered with corticosteroids, anti-IL-6 antibodies, tocilizumab, anti-IL-1 antibodies, cyclosporine, antiepileptics, benzodiazepines, acetazolamide, hyperventilation therapy, or hyperosmolar therapy, or any combination thereof.

[08] In another example, the immunotherapy-related toxicity comprises a brain disease, damage or malfunction. In a related example, the brain disease, damage or malfunction comprises CAR-T cell related neurotoxicity or CAR-T cell related encephalopathy syndrome (CRES). In a related example, 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 the subject. In another example, the immunotherapy-related toxicity comprises CAR-T induced Cytokine Release Syndrome (CRS). In a related example, inhibiting or reducing incidence of CRS comprises reducing or inhibiting, without limitation, high fever, myalgia, nausea, hypotension, hypoxia, or shock, or a combination thereof. In a related example, the immunotherapy-related toxicity is life-threatening.

[09] In another example, the serum concentration of ANG2 or VWF, or the serum ANG2:ANG1 ratio of the subject is reduced. In a related example, the subject has a body temperature above 38°C, an IL-6 serum concentration > 16 pg/ml, or an MCP-1 serum concentration above 1,300 pg/ml during the first 36 hours after infusion of said CAR-T cells. In a related example, the subject is predisposed to have said brain disease, damage or malfunction. In a related example, the subject has an ANG2:ANG1 ratio in serum above 1 prior to the infusion of said CAR-T cells.

[010] In another example, the immunotherapy-related toxicity comprises hemophagocytic lymphohistiocytosis (HLH) or macrophage-activation syndrome (MAS). In a related example, 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 IFNγ in the peripheral circulation, or

reducing the concentration of GM-CSF in the peripheral circulation, or any combination thereof.

[011] In another example, the 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. In a related example, the subject is predisposed to acquiring HLH or MAS. In a related example, the 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.

[012] In one example, the GM-CSF antagonist is an anti-humanGM-CSF antibody (anti-hGM-CSF antibody). In another example, the anti-GM-CSF antibody blocks binding of GM-CSF to the alpha subunit of the GM-CSF receptor. In another example, the anti-GM-CSF antibody is a polyclonal antibody. In another example, the anti-GM-CSF antibody is a monoclonal antibody. In another example, the anti-hGM-CSF antibody is an antibody fragment that is a Fab, a Fab', a F(ab')2, a scFv, or a dAB. In some examples, the monoclonal anti-hGM-CSF antibody, the single-chain Fv, and the Fab may be generated in the chicken; chicken IgY are avian equivalents of mammalian IgG antibodies. (Park *et al*., Biotechnology Letters (2005) 27:289-295; Finley *et al*., Appl. Environ. Microbiol., May 2006, p. 3343–3349). Chicken IgY antibodies have the following advantages: higher avidity, i.e., overall strength of binding between an antibody and an antigen, higher specificity (less cross reactivity with mammalian proteins other than the immunogen); high yield in the egg yolk, and lower background (the structural difference in the Fc region of IgY and IgG results in less false positive staining). In another example, the anti-hGM-CSF antibody may be a camelid, e.g., a llama-derived single variable domain on a heavy chain antibodies lacking light chains (also called sdAbs, VHHs and Nanobodies®); the VHH domain (about 15 kDa) is the smallest known antigen recognition site that occurs in mammals having full binding capacity and affinities (equivalent to conventional antibodies). (Garaicoechea *et al*. (2015) PLoS ONE 10(8): e0133665; Arbabi-Ghahroudi M (2017) Front. Immunol. 8:1589; Wu *et al*., Translational Oncology (2018) 11, 366–373). In another example, the antibody fragment is conjugated to polyethylene glycol. In another example, the anti-GM-CSF antibody has an affinity ranging from about 5 pM to about 50

pM. In another example, anti-GM-CSF antibody is a neutralizing antibody. In another example, the anti-GM-CSF antibody is a recombinant or chimeric antibody. In another example, the anti-GM-CSF antibody is a human antibody. In another example, the anti-GM-CSF antibody comprises a human variable region. In another example, the anti-GM-CSF antibody comprises an engineered human variable region. In another example the anti-GM-CSF antibody comprises a humanized variable region. In another example, the anti-GM-CSF antibody comprises an engineered human variable region. In another example the anti-GM-CSF antibody comprises a humanized variable region.

[013] In one example, the anti-GM-CSF antibody comprises a human light chain constant region. In another example, the anti-GM-CSF antibody comprises a human heavy chain constant region. In another example, the human heavy chain constant region is a gamma chain. In another example, the anti-GM-CSF antibody binds to the same epitope as chimeric 19/2. In another example, the anti-GM-CSF antibody comprises the VH region CDR3 and VL region CDR3 of chimeric 19/2. In another example, the anti-GM-CSF antibody comprises the VH region and VL region CDRl, CDR2, and CDR3 of chimeric 19/2.

[014] In one example, the anti-GM-CSF antibody comprises a heavy chain variable region that comprises a CDR3 binding specificity determinant RQRFPY or RDRFPY, a J segment, and a V-segment, wherein the J-segment comprises at least 95% identity to human JH4 (YFDYWGQGTLVTVSS) and the V-segment comprises at least 90% identity to a human germ line VH1 1-02 or VH1 1-03 sequence; or a heavy chain variable region that comprises a CDR3 binding specificity determinant comprising RQRFPY. In another example, the J segment comprises YFDYWGQGTLVTVSS. In another example, the CDR3 comprises RQRFPYYFDY or RDRFPYYFDY. In another example, the heavy chain variable region CDR1 or CDR2 can be a human germline VH1 sequence; or both the CDR1 and CDR2 can be human germline VH1. In another example, the antibody comprises a heavy chain variable region CDR1 or CDR2, or both CDR1 and CDR2, as shown in a V_H region set forth in Figure 1. In another example, the anti-GM-CSF antibody has a V-segment that has a V_H V-segment sequence shown in Figure 1. In another example, the V_H that has the sequence of VH#1, VH#2, VH#3, VH#4, or VH#5 set forth in Figure 1.

[015] In another example, the anti-GM-CSF antibody, *e.g.,* that has a heavy chain variable region as described in the paragraph above, comprises a light chain variable region that comprises a CDR3 binding specificity determinant comprising the amino acid sequence FNK or FNR.

[016] In another example, the anti-GM-CSF antibody comprises a VL region that comprises a CDR3 comprising the amino acid sequence FNK or FNR. In one example, the anti-GM-CSF antibody comprises a human germline JK4 region. In another example, the antibody V_L region CDR3 comprises QQFN(K/R)SPLT. In another example, the anti-GM-CSF antibody comprises a VL region that comprises a CDR3 comprising QQFNKSPLT. In another example, the VL region comprises a CDRl, or a CDR2, or both a CDR1 and CDR2, of a V_L region shown in Figure 1. In another example, the V_L region comprises a V segment that has at least 95% identity to the VKIIIA27 V-segment sequence as shown in Figure 1. In another example, the V_L region has the sequence of VK#1, VK#2, VK#3, or VK#4 set forth in Figure 1.

[017] In one example, the anti-GM-CSF antibody has a VH region CDR3 binding specificity determinant RQRFPY or RDRFPY and a VL region that has a CDR3 comprising QQFNKSPLT. In another example, the anti-GM-CSF antibody has a VH region sequence set forth in Figure 1 and a VL region sequence set forth in Figure 1. In another example, the VH region or the VL region, or both the VH and VL region amino acid sequences comprise a methionine at the N-terminus. In another example, the GM-CSF antagonist is selected from the group comprising of an anti-GM-CSF receptor antibody or a soluble GM-CSF receptor, a cytochrome b562 antibody mimetic, a GM-CSF peptide analog, an adnectin, a lipocalin scaffold antibody mimetic, a calixarene antibody mimetic, and an antibody like binding peptidomimetic.

[018] In one example, disclosed herein is a method of increasing the efficacy of CAR-T immunotherapy in a subject, the method comprising a step of administering a recombinant GM-CSF antagonist to the subject, wherein said administering increases the efficacy of CAR-T immunotherapy in said subject. In another example, said administering a recombinant GM-CSF antagonist occurs prior to, concurrent with, or following said CAR-T immunotherapy. In another example, said increased efficacy comprises increased CAR-T cell expansion, reduced myeloid-derived suppressor cell (MDSC) number that inhibit T-

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.

[018a] In one aspect, disclosed herein is a use of a recombinant hGM-CSF antagonist in the manufacture of a medicament for increasing the efficacy of CAR-T immunotherapy in a subject, wherein the administration of the medicament increases the efficacy of CAR-T immunotherapy in said subject.

[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,

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.

[022] In another example, the inhibiting or reducing the incidence or the severity of CAR-T related toxicity comprises preventing the onset of CAR-T related toxicity.

[023] In another example, disclosed herein is a method of blocking or reducing GM-CSF expression in a cell, comprising knocking out or silencing GM-CSF gene expression in a cell. In an example, the blocking or reducing of GM-CSF expression comprises short interfering RNS (siRNA), CRISPR, RNAi, DNA-directed RNA interference (ddRNAi), which is a gene-silencing technique that uses DNA constructs to activate an animal cell's endogenous RNA interference (RNAi) pathways, or targeted genome editing with engineered transcription activator-like effector nucleases (TALENs), i.e., artificial proteins composed of a customizable sequence-specific DNA-binding domain fused to a nuclease that cleaves DNA in a nonsequence-specific manner. (Joung and Sander, Nat Rev Mol Cell Biol. 2013 January; 14(1): 49–55), which is incorporated herein in its entirety by reference. In an example, the cell is a CAR-T cell.

[023a] In another aspect, disclose herein is a method of blocking or reducing hGM-CSF expression in a cell, comprising knocking out or silencing hGM-CSF gene expression in the cell.

[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 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 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 that 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 and a control antibody.

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 the serum concentration of ANG2 or VWF, or the 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 hGM-CSF antagonist is an anti-hGM-CSF antibody.

26. The use of claim 25, wherein the anti-hGM-CSF antibody blocks binding of hGM-CSF to the alpha subunit of the hGM-CSF receptor.

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

28. The use of any of claims 25 or 26, wherein the anti-hGM-CSF antibody is a monoclonal antibody.

29. The use of any of claims 25-28, wherein the anti-hGM-CSF antibody is an antibody fragment that is a Fab, a Fab', a F(ab')2, a scFv, or a dAB.

30. The use of claim 29, wherein the antibody fragment is conjugated to polyethylene glycol.

31. The use of any of claims 25-30, wherein the anti-hGM-CSF antibody has an affinity ranging from about 5 pM to about 50 pM.

32. The use of any of claims 25-31, wherein the anti-hGM-CSF antibody is a neutralizing antibody.

33. The use of any of claims 25-32, wherein the anti-hGM-CSF antibody is a recombinant or chimeric antibody.

34. The use of any of claims 25-33, wherein the anti-hGM-CSF antibody is a human antibody.

35. The use of any of claims 25-33, wherein the anti-hGM-CSF antibody comprises a human variable region.

36. The use of any of claims 25-33, wherein the anti-hGM-CSF antibody comprises a human light chain constant region.

37. The use of any of claims 25-36, wherein the anti-hGM-CSF antibody comprises a human heavy chain constant region.

38. The use of claim 37, wherein the human heavy chain constant region is a gamma chain.

39. The use of any of claims 25-38, wherein the anti-hGM-CSF antibody binds to the same epitope as chimeric 19/2.

40. The use of any of claims 25-38, wherein the anti-hGM-CSF antibody comprises the VH region CDR3 and VL region CDR3 of chimeric 19/2.

41. The use of any of claims 25-38, wherein the anti-hGM-CSF antibody comprises the VH region and VL region CDRl, CDR2, and CDR3 of chimeric 19/2.

42. The use of any of claims 25-38, wherein the anti-hGM-CSF antibody comprises a VH region that comprises a CDR3 binding specificity determinant RQRFPY or RDRFPY, a J segment, and a V-segment, wherein the J-segment comprises at least 95% identity to human JH4 (YFD YWGQGTL VTVSS) and the V-segment comprises at least 90% identity to a human germ line VHl 1-02 or VHl 1-03 sequence; or a VH region that comprises a CDR3 binding specificity determinant RQRFPY.

43. The use of claim 42, wherein the J segment comprises YFDYWGQGTLVTVSS.

44. The use of any of claims 42 or 43, wherein the CDR3 comprises RQRFPYYFDY or RDRFPYYFDY.

45. The use of any of claims 42-44, wherein the VH region CDRl is a human germline VHl CDRl; the VH region CDR2 is a human germline VHl CDR2; or both the CDRl and CDR2 are from a human germline VHl sequence.

46. The use of any of claims 42-44, wherein the anti-hGM-CSF antibody comprises a VH CDRl , or a VH CDR2, or both a VH CDRl and a VH CDR2 as shown in a VH region set forth in Figure 1.

47. The use of any of claims 42-44, wherein the V-segment sequence has a VH V segment sequence shown in Figure 1.

48. The use of any of claims 42-44, wherein the VH has the sequence of VH#1, VH#2, VH#3 , VH#4, or VH#5 set forth in Figure 1.

49. The use of any of claims 25-48, wherein the anti-hGM-CSF antibody comprises a VL-region that comprises a CDR3 comprising the amino acid sequence FNK or FNR.

50. The use of claim 49, wherein the anti-hGM-CSF antibody comprises a human germline JK4 region.

51. The use of claim 49 or claim 50, wherein the VL region CDR3 comprises QQFN(K/R)SPLT.

52. The use of claim 51, wherein the anti-hGM-CSF antibody comprises a VL region that comprises a CDR3 comprising QQFNKSPLT.

53. The use of any of claims 49-52, where the VL region comprises a CDRl , or a CDR2, or both a CDRl and CDR2 of a VL region shown in Figure 1.

54. The use of any of claims 49-53, wherein the VL region comprises a V segment that has at least 95% identity to the VKIII A27 V-segment sequence as shown in Figure 1.

55. The use of claim 49, wherein the VL region has the sequence of VK# 1 , VK#2, VK#3 , or VK#4 set forth in Figure 1.

56. The use of any of claims 25-38, wherein the anti-hGM-CSF antibody has a VH region CDR3 binding specificity determinant RQRFPY or RDRFPY and a VL region that has a CDR3 comprising QQFNKSPLT.

57. The use of any of claims 25-38, wherein the anti-hGM-CSF antibody has a VH region sequence set forth in Figure 1 and a VL region sequence set forth in Figure 1.

58. The use of any of claims 25-57, 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.

59. The use of any one of claims 1 to 24, wherein the hGM-CSF antagonist is selected from the group comprising of an anti-hGM-CSF receptor antibody or a soluble hGM-CSF receptor, a cytochrome b562 antibody mimetic, a hGM-CSF peptide analog, an adnectin, a lipocalin scaffold antibody mimetic, a calixarene antibody mimetic, and an antibody like binding peptidomimetic.

60. Use of a recombinant hGM-CSF antagonist in the manufacture of a medicament for increasing the efficacy of CAR-T immunotherapy in a subject, wherein the administration of the medicament increases the efficacy of CAR-T immunotherapy in said subject.

61. The use of claim 60, wherein administration of said medicament is to occur prior to, concurrent with, or following said CAR-T immunotherapy.

62. The use of claim 61, wherein said increased efficacy comprises increased CAR-T cell expansion, reduced myeloid-derived suppressor cells (MDSC) that inhibit T-cell function, synergy with a checkpoint inhibitor, or any combination thereof.

63. The use of claim 62, wherein said increased CAR-T cell expansion comprises at least a 50% increase compared to a control.

64. The use of claim 63, wherein said increased CAR-T cell expansion comprises at least a one quarter log expansion compared to a control.

65. The use of claim 62, wherein said increased cell expansion comprises at least a one half log expansion compared to a control.

66. The use of claim 62, wherein said increased cell expansion comprises at least a one log expansion compared to a control.

67. The use of claim 62, wherein said increased cell expansion comprises a greater than one log expansion compared to a control.

68. The use of any one of claims 60-67, wherein the hGM-CSF antagonist comprises a neutralizing antibody.

69. The use of claim 68, wherein the neutralizing antibody is a monoclonal antibody.

70. 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.

71. The use of claim 70, wherein said CAR-T related toxicity comprises neurotoxicity, CRS, or a combination thereof.

72. The use of claim 71, 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 and a control antibody.

73. The use of claim 70-72, wherein 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 hGM-CSF, or any combination thereof.

74. The use of any of claims 70-72, 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.

75. The use of any of claims 70-74, wherein the inhibiting or reducing the incidence or the severity of CAR-T related toxicity comprises preventing the onset of CAR-T related toxicity.

76. A method of blocking or reducing hGM-CSF expression in a cell, comprising knocking out or silencing hGM-CSF gene expression in the cell.

77. The method of claim 76, wherein the blocking or reducing hGM-CSF expression comprises siRNA, CRISPR, RNAi, ddRNAi or TALENs.

78. The method of any of claims 1-74, wherein the subject is a human.