MULTIFUNCTIONAL MOLECULES BINDING TO TCR AND USES THEREOF

CROSS REFERENCE

[0001] This application claims the benefits of U.S. Provisional Application No. 63/379,271, filed October 12, 2022, and U.S. Provisional Application No. 63/381,231, filed October 27, 2022, each of which is incorporated herein by reference in its entirety.

BACKGROUND

[0002] Currently available molecules designed to redirect T cells to promote tumor cell lysis for cancer immunotherapy typically target the CD3 epsilon (CD3e) subunit of the T cell receptor (TCR). However, there are limitations to this approach. Previous studies have shown that, e.g., low doses of anti-CD3e monoclonal antibody (mAb) can cause T cell dysfunction and exert immunosuppressive effects. In addition, anti-CD3e mAbs bind to all T cells and thus activate a large number of T cells. Such non-physiological massive activation of T cells by these anti-CD3e mAbs can result in the production of proinflammatory cytokines such as IFN-gamma, IL-1-beta, IL-6, IL-10 and TNF-alpha, causing a "cytokine storm" known as the cytokine release syndrome (CRS), which is also associated with neurotoxicity (NT). Thus, there is a need for improved T cell receptor-binding molecules that redirect T cells for cancer immunotherapy.

SUMMARY

[0002a] In one aspect, provided herein is use of a multifunctional molecule in the manufacture of a medicament for treating cancer in a human subject in need thereof, wherein the multifunctional molecule comprises: (a) a TCRβV6-binding moiety, and (b) an interleukin-2 (IL-2) or a functional fragment or a functional variant thereof, and wherein the multifunctional molecule is to be administered to the human subject at a first dose of from 0.001 mg/kg to 10 mg/kg; thereby treating the cancer in the human subject.

[0002b] In another aspect, provided herein is use of a pharmaceutical composition comprising a multifunctional molecule in the manufacture of a medicament for treating cancer in a human subject in need thereof, wherein the multifunctional molecule comprises: (a) a TCRβV6-binding moiety, and (b) an interleukin-2 (IL-2) or a functional fragment or a functional variant thereof, and wherein the pharmaceutical composition comprising the multifunctional molecule is to be administered to the human subject, wherein the multifunctional molecule is to be administered to the human subject at a first dose of from 0.001 mg/kg to 10 mg/kg; thereby treating the cancer in the human subject, and wherein the pharmaceutical composition further comprises a pharmaceutically acceptable excipient, carrier or diluent.

[0002c] In another aspect, provided herein is a dose of a pharmaceutical composition comprising a multifunctional molecule, wherein the multifunctional molecule comprises: (a) a TCRβV6-binding moiety, and (b) an interleukin-2 (IL-2) or a functional fragment or variant thereof; and wherein the dose is from 0.001 mg/kg to 10 mg/kg of the multifunctional molecule.

[0002d] In another aspect, a pharmaceutical composition comprising a multifunctional molecule and a pharmaceutically acceptable diluent, wherein the multifunctional molecule comprises: (a) a TCRβV6-

binding moiety, and (b) an interleukin-2 (IL-2) or a functional fragment or variant thereof; wherein the pharmaceutically acceptable diluent is a 0.9% saline solution; and wherein the multifunctional molecule is present in the pharmaceutical composition at a concentration of from 0.02 mg/mL to 15 mg/mL.

[0003] Provided herein is a method of treating cancer in a human subject in need thereof comprising administering to the human subject a multifunctional molecule, wherein the multifunctional molecule comprises a TCRβV6-binding moiety, and an interleukin-2 (IL-2) or a functional fragment or a functional variant thereof, wherein the multifunctional molecule is administered to the human subject at a first dose of from about 0.001 mg/kg to about 10 mg/kg; thereby treating the cancer in the human subject.

[0004] Also provided herein is a method of treating cancer in a human subject in need thereof comprising administering to the human subject a multifunctional molecule, wherein the multifunctional molecule comprises a TCRβV6-binding moiety, and an interleukin-2 (IL-2) or a functional fragment or a functional variant thereof, wherein administering comprises administering multiple doses of the multifunctional molecule to the human subject.

[0005] Also provided herein is a method of treating cancer in a human subject in need thereof comprising administering to the human subject a first dose of a multifunctional molecule, wherein the multifunctional molecule comprises a TCRβV6-binding moiety, and an interleukin-2 (IL-2) or a functional fragment or a functional variant thereof, wherein the human subject is characterized as having a solid tumor, and wherein if the human subject had a symptomatic central nervous system (CNS) metastases, the human subject has previously been treated for the symptomatic central nervous system (CNS) metastases, has been asymptomatic for 14 days or more and is not currently receiving treatment for CNS disease, and does not currently have leptomeningeal disease or cord compression; and if the human subject had previously