

PRIORITY

[0001] This application claims the benefit of U.S. Provisional Patent Application Nos. 63/067,834, filed August 19, 2020 and 63/092,272, filed October 15, 2020 which are hereby incorporated by reference in their entireties.

SEQUENCE LISTING INCORPORATION PARAGRAPH

[0002] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on August 19, 2021, is named 067461-5272-WO_SL.txt and is 1,130,417 bytes in size.

BACKGROUND

[0003] The natural immune response against tumor dispatches immune effector cells such as natural killer (NK) cells and T cells to attack and destroy tumor cells. Tumor infiltrating lymphocytes (TILs) often express multiple immune checkpoint receptors (e.g., PD-1, CTLA-4) and costimulatory receptors (e.g., ICOS, 4-1BB, OX40, GITR, and CD28). TILs lose their cytotoxic ability over time due to upregulation of inhibitory immune checkpoints. While checkpoint blockade has demonstrated increased clinical response rates relative to other treatment options, many patients still fail to achieve a response to checkpoint blockade. Engagement of costimulatory receptors on TILs could provide a positive signal capable of overcoming negative signals of immune checkpoints. Preclinical and clinical studies of agonistic costimulatory receptor antibodies have indeed demonstrated that agonism of costimulatory receptors can result in impressive anti-tumor responses, activating T cells to attack tumor cells.

[0004] It is also important for cancer therapy to enhance anti-tumor activity by specifically destroying tumor cells while minimizing peripheral toxicity. In this context, it is crucial that only T cells in the presence of the target tumor cells are provided a costimulatory signal. However, agonism of costimulatory receptors with monospecific full-length antibodies is likely nondiscriminatory with regards to TILs vs. peripheral T cells vs. autoantigen-reactive T cells that contribute to autoimmune toxicities. For instance, urelumab, a monospecific, nondiscriminatory, pan-4-1BB agonist antibody, exhibited significant liver toxicity in early