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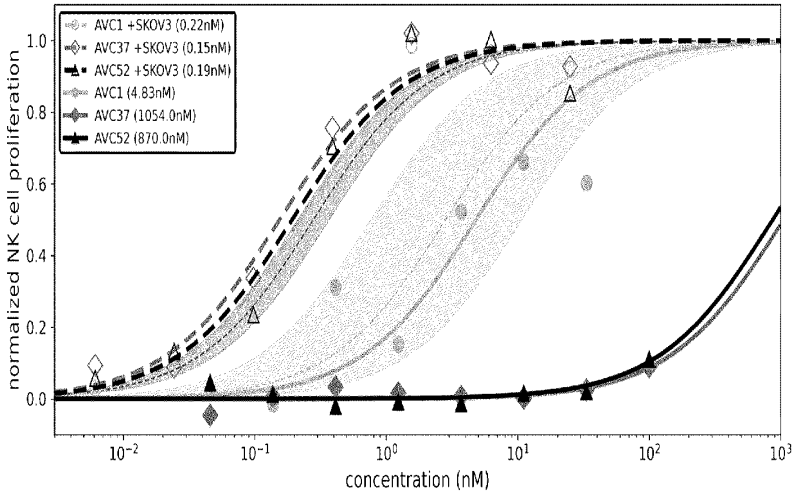
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(54) Title: MUTEINS OF 4-1BB LIGAND EXTRACELLULAR DOMAIN, FUSION PROTEINS COMPRISING THE SAME AND USES THEREOF

Fig. 1



(57) **Abstract:** The present invention relates to 4-1BB ligand (4-BBL) extracellular domain (ECD) muteins having reduce affinity for its cognate receptor 4-1BB. The 4-1BBL ECD muteins can be present in homo- or heterotrimeric fusion protein comprising three 4-1BBL ECD monomers. The invention further relates conjugates of such the 4-BBL ECD muteins with a heterologous moiety, such as an antigen binding protein. The antigen-binding regions comprised in the antigen binding protein in the conjugates preferably are specific for a tumor-associated antigen (TAA). In addition to a 4-BBL ECD mutein, the conjugates can comprise further NK cell-activating cytokines, such an IL-21 receptor agonist. The conjugates can further comprise an antigen-binding region that has affinity for a surface antigen expressed on NK cells, e.g. CD16A. Alternatively, the conjugates can further comprise an antigen-binding region that specifically binds an epitope of a γδ TCR. The conjugates of the invention specifically redirect and activate NK cells or γδ T cells to lyse targeted tumor cells. The invention further relates to the use of the 4-BBL ECD muteins and conjugates thereof in the treatment

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of cancer, preferably a cancer expressing the TAA.