observed any cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS) or other toxicity associated with the CAR-NK cell product.[7] The present disclosure concerns expansion of the CAR-NK cell platform to target other cancer antigens, including CD5, to broaden the clinical impact of this therapy.

[0004] Multiple studies have demonstrated that the choice of co-stimulatory domain in CAR-T cells influences their function, persistence and metabolic profile.[8-10] In the field of CAR-NK cells, the first constructs tested in the clinic have incorporated CD28, a T cell specific co-stimulatory domain, borrowing from the design of CAR-T cells. There are some preclinical CAR-NK cell studies looking at the function of various NK specific co-stimulatory molecules, but there are no studies looking systematically at the impact of co-stimulatory domains on the proliferation, transcriptomic and proteomic profile, polyfunctionality, metabolism and fitness of the NK cells. In the present disclosure, it was aimed to do so, by comprehensively studying the impact of co-stimulatory domains including some that are more relevant for NK cell biology, namely DNAX-activating Protein 10 (DAP10), a major adaptor protein and the exclusive signaling intermediate of NKG2D in human NK cells, DNAX-activating Protein 12 (DAP12), an important adaptor molecule that associates with multiple activating receptors (e.g. NKG2C, NKp44, activating KIRs) and NKG2D, one of the most potent NK cytotoxicity receptors which is essential for anti-tumor immunity.[11] The results show that CD5 CAR-NK cells with DAP10 co-stimulatory molecule perform significantly better *in vitro* and *in vivo* and show enhanced polyfunctionality, metabolic fitness and memory like characteristics which augment their anti-tumor activity compared to CD5 CAR-NK cells containing other co-stimulatory molecules. Based on these preclinical data, a Phase I/II clinical trial evaluating the safety and efficacy of CD5-DAP10-CD3ζ CAR-NK cells is in preparation.

[0005] Thus, the present disclosure, in particular embodiments, concerns methods and compositions concerning genetical engineering of cells for adoptive cell therapy, including human NK cells, to target cancers including CD5-positive cancers.

BRIEF SUMMARY

[0005a] In one aspect, provided herein is an expression construct comprising sequence that encodes a CD5-specific engineered receptor, wherein said receptor comprises CD28 transmembrane domain (TM) and CD28 intracytoplasmic domain (ICD).

[0005b] In another aspect, provided herein is a vector, comprising the expression construct as described herein.

[0005c] In another aspect, provided herein is an immune cell, comprising the expression construct as described herein or the vector as described herein.

[0005d] In another aspect, provided herein is a population of immune cells as described herein, said cells present in a suitable medium.

[0005e] In another aspect, provided herein is use of cells harboring the expression construct as described herein in the manufacture of a medicament for killing CD5- positive cells in an individual, wherein an effective amount of cells harboring the expression construct as described herein is to be administered to the individual.

[0005f] In another aspect, provided herein is use of cells harboring the expression construct as described herein in the manufacture of a medicament for preventing cancer or preventing metastasis of cancer in an individual, wherein a therapeutically effective amount of cells harboring the expression construct as described herein is to be administered to the individual.

[0005g] In another aspect, provided herein is the cells harboring the expression construct as described herein for use in therapy.

[0006] Embodiments of the disclosure encompass methods and compositions related to engineered cellular receptors that target CD5 (also known as cluster of differentiation 5 or LEU1 or T1, for example). In specific embodiments, the engineered receptors that target CD5 are in the form of polynucleotides, polypeptides, or are comprised on the surface of cells of any kind,