disclosed in WO2024138181A2, whose content is incorporated in its entirety by reference) that specifically targets certain diseases (such as tumors). Optionally, the immune cell may further express a targeting polypeptide, which may comprise at least one of a CAR, a TCR, or an Aspire-TCR that can specifically and selectively recognize and bind certain target molecule/protein/marker on the surface of target cells (e.g. tumor cells) or on the surface of other entities (e.g. bacteria, fungi, viruses).

[0066] Sixthly, a culturing method for the immune cell as described above is also provided. The method comprises the steps of:

[0067] (1) obtaining an engineered immune cell from an immune cell, such that the engineered immune cell expresses the synthetic cytokine signaling system according to any embodiment as described above; and

[0068] (2) culturing the engineered immune cell in a medium containing none or reduced level of a cytokine supplement *in vitro*.

[0069] Herein, the "reduced level of a cytokine supplement" as used herein, means a level of the cytokine supplement used for *in vitro* culture of the immune cell that is at least 50% less than the level of the cytokine supplement that is conventionally used for the *in vitro* culture of an unmodified immune cell. Herein, the conventional level of IL-2 supplement that is used for the *in vitro* culture of unmodified T cells or TILs is approximately 300 IU/mL, and "a reduced level of IL2" means a level of IL2 used for the *in vitro* culture is 150 IU/mL or less (e.g. 150 IU/mL, 120 IU/mL, 100 IU/mL, 80 IU/mL, 60 IU/mL, 50 IU/mL, 25 IU/mL, 10 IU/mL, 5 IU/mL, etc.).

[0070] Herein step (1) can be realized by introducing into the immune cell the vector kit according to any embodiments as described above.

[0071] In step (2), the cytokine supplement may comprise at least one of IL-2, IL-4, IL-7, IL-9, IL-15, or IL-21. Thus according to some embodiment, the culturing medium may lack IL-2, may lack IL-15, or may lack any of the above cytokines (i.e. IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21). According to some embodiments, the cytokine supplement may only consist of IL-2.

[0071a] In another aspect, the present disclosure provides use of a population of engineered immune cells in the manufacture of a medicament for treating a disease in a subject, wherein each of the population of the engineered immune cells expresses the synthetic cytokine signaling system as described herein; optionally wherein each of the engineered immune cells has been obtained from an immune cell; and cultured in a medium containing none or a reduced level of a cytokine *supplement in vitro* to thereby obtain the population of the engineered immune cells; optionally wherein the engineered immune cell further expresses a targeting

polypeptide, wherein the targeting polypeptide comprises at least one of a chimeric antigen receptor (CAR), a T cell receptor (TCR), or an Aspire-T cell receptor; optionally wherein the immune cell is any of a T cell, a γδ T cell, a natural killer (NK) cell, a natural killer T (NKT) cell, or a tumor-infiltrating lymphocyte (TIL), or an engineered immune cell derived therefrom; and optionally wherein the disease is a cancer, an autoimmune disease, or a viral infection.

[0072] Seventhly, the present disclosure further provides a method for treating a disease in a subject in need thereof, comprising: administering a plurality of engineered immune cells into the subject, wherein each of the plurality of engineered immune cells expresses the synthetic cytokine signaling system according to any embodiments as described above.

[0073] Herein, the treating method may comprise: administering to the subject a therapeutically effective number of the engineered immune cells to treat the disease.

[0074] The term "subject" as used herein refers to an animal such as a mammal, which can