

**CLAIMS**

1. An immune cell expressing a chimeric antigen receptor (CAR),  
  
wherein the CAR comprises an intracellular signaling domain comprising a signaling domain or fragment of a CD28 protein that is functional in the absence of lymphocyte-specific protein tyrosine kinase (LCK), and  
  
wherein the immune cell comprises or has been contacted with a nucleic acid sequence capable of downregulating or eliminating gene expression of LCK, such that the expression and/or function of LCK has been reduced or eliminated.
2. The immune cell of claim 1, wherein the immune cell is a T cell or an NK cell.
3. The immune cell of claim 1, wherein the nucleic acid sequence capable of downregulating gene expression of LCK is selected from the group consisting of an antisense RNA, antagomir RNA, siRNA, shRNA, a CRISPR system, a zinc finger nuclease system and a transcription activator-like effector based nuclease (TALEN) system.
4. The immune cell of claim 1, wherein the immune cell comprises a vector comprising a nucleic acid encoding the CAR.
5. The immune cell of claim 1, wherein the immune cell comprises a vector comprising a nucleic acid encoding an inhibitor of LCK capable of downregulating or eliminating gene expression or modifying the function of LCK.
6. The immune cell of claim 1, wherein the immune cell comprises a vector comprising a nucleic acid encoding the CAR and a nucleic acid encoding an inhibitor of LCK capable of downregulating or eliminating gene expression of LCK.
7. The immune cell of claim 1, wherein the CAR comprises an extracellular antigen-binding domain.

8. The immune cell of claim 1, wherein the intracellular signaling domain further comprises a primary-signaling domain comprising a functional signaling domain of a protein selected from CD3 zeta, CD3 gamma, CD3 delta, CD3 epsilon, FcR gamma, Fc epsilon RI beta, CD79a, CD79b, Fc gamma RIIa, DAP10, or DAP12.
9. An immune cell expressing a CAR, wherein the immune cell has been modified such that expression of the LCK gene has been disrupted.
10. A method of manufacturing the immune cell of claim 1, the method comprising contacting an immune cell with an inhibitor of LCK for a sufficient time and under conditions to downregulate or eliminate the gene expression and/or function of LCK, wherein the inhibitor of LCK is a nucleic acid sequence.
11. The method of claim 10, wherein the inhibitor of LCK is a nucleic acid sequence capable of downregulating gene expression of LCK.
12. The method of claim 11, wherein the inhibitor of LCK is a CRISPR system.
13. The method of claim 10, wherein the method further comprises introducing a nucleic acid encoding a CAR into the immune cell.
14. A vector system comprising 1) a vector comprising a nucleic acid sequence encoding an inhibitor of LCK and 2) a vector comprising a nucleic acid sequence encoding a CAR.
15. A vector comprising a nucleic acid sequence encoding an inhibitor of LCK and a nucleic acid sequence encoding a CAR.
16. An *ex vivo* method of improving the efficacy of a CAR-expressing immune cell in a cell therapy, the method comprising contacting the CAR-expressing immune cell with an inhibitor of LCK for a sufficient time and under conditions to reduce or eliminate the gene expression and/or function of LCK, wherein the inhibitor of LCK is a nucleic acid sequence.

17. The method of claim 16, wherein the CAR-expressing immune cell is a Car-expressing T (CART) cell.
18. An immune cell according to any one of claims 1-9 for use in treating a subject in need thereof.
19. Use of an immune cell according to any one of claims 1-9 in the manufacture of a medicament for treating a subject in need, wherein the subject has a disease associated with expression of an antigen, in particular a proliferative disease, a precancerous condition, a cancer, or a non-cancer related indication associated with expression of the tumor antigen, an infectious disease or an autoimmune disease.