

CLAIMS

1. An isolated nucleic acid encoding a chimeric adaptor (CAD) polypeptide, wherein the CAD polypeptide comprises a DAP10 domain comprising a human DAP10 amino acid sequence and at least one costimulatory domain, wherein said CAD polypeptide specifically lacks an ectodomain comprising a functional extracellular receptor and/or ligand-binding domain.
2. The isolated nucleic acid according to claim 1, wherein the costimulatory domain is selected from TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9, TLR10, CARD11, CD2, CD3C, CD7, CD27, CD28, CD30, CD40, CD54 (ICAM), CD70, CD80, CD83, CD86, CD134 (OX40), CD137 (4-1BB), CD278 (ICOS), FcR, LAT, NKD2C, SLP76, TRIM, and ZAP70, or combinations thereof.
3. The isolated nucleic acid according to claim 2, wherein the at least one costimulatory domain is 4-1BB.
4. The isolated nucleic acid according to claim 2, wherein the at least one costimulatory domain is CD28.
5. The isolated nucleic acid according to any one of claims 1-4, wherein said CAD polypeptide further comprises at least one intracellular signaling domain, wherein the at least one intracellular signaling domain is selected from CD3 ζ , DAP12, LFA-1, and CD3t.
6. The isolated nucleic acid according to claim 5, wherein the at least one signaling domain is CD3 ζ , optionally wherein CD3 ζ has an amino acid sequence set forth as SEQ ID NO: 76.
7. The isolated nucleic acid according to any one of claims 1-6, wherein the at least one costimulatory domain is 4-1BB and the intracellular signaling domain is CD3 ζ .

8. The isolated nucleic acid according to claim 7, wherein said CAD polypeptide comprises, from N-terminus to C-terminus, the DAP10 domain, the 4-1BB costimulatory domain followed by the CD3 ζ intracellular signaling domain.
9. The isolated nucleic acid according to claim 1, wherein said CAD polypeptide comprises a 4-1BB costimulatory domain and a CD28 costimulatory domain.
10. The isolated nucleic acid according to claim 9, wherein said CAD polypeptide comprises, from N-terminus to C-terminus, the DAP10 domain, the 4-1BB costimulatory domain followed by the CD28 costimulatory domain, followed in turn by a CD3 ζ intracellular signaling domain, optionally wherein CD3 ζ has an amino acid sequence set forth as SEQ ID NO: 76.
11. The isolated nucleic acid according to claim 9, wherein said CAD polypeptide comprises, from N-terminus to C-terminus, the DAP 10 domain, the CD28 costimulatory domain followed by the 4-1BB costimulatory domain, followed in turn by a CD3 ζ signaling domain, optionally wherein CD3 ζ has an amino acid sequence set forth as SEQ ID NO: 76.
12. The isolated nucleic acid according to any one of claims 1-11, wherein the human DAP 10 amino acid sequence comprises an amino acid sequence having at least 90%, 95%, 97%, or 99% sequence identity to SEQ ID NO: 1.
13. The isolated nucleic acid according to claim 12, wherein the human DAP10 amino acid sequence comprises a mutated human DAP 10 amino acid sequence.
14. The isolated nucleic acid according to claim 13, wherein the mutated human DAP10 amino acid sequence comprises amino acid substitutions at positions corresponding to K84 and/or Y86.
15. The isolated nucleic acid according to claim 14, wherein the amino acid substitution at position K84 comprises a K84R substitution.

16. The isolated nucleic acid according to claim 14 or claim 15, wherein the amino acid substitution at position Y86 comprises a Y86F substitution.
17. The isolated nucleic acid according to any one of claims 1-16, wherein the isolated nucleic acid is operably linked to a regulatable promoter.
18. The isolated nucleic acid according to any one of claims 1-17, wherein said isolated nucleic acid further encodes for a cytokine.
19. The isolated nucleic acid according to claim 18, wherein the cytokine is selected from the group consisting of IL-2, IL-4, IL-7, IL- 15, IL-21, IL-23.
20. An expression vector comprising the isolated nucleic acid of any one of claims 1-19.
21. A chimeric adaptor (CAD) polypeptide encoded by the isolated nucleic acid according to any one of claims 1-19, or the expression vector according to claim 20.
22. A mammalian cell comprising the expression vector of claim 20, or the CAD polypeptide according to claim 21, wherein the mammalian cell expresses at least one receptor that associates with DAP 10.
23. The mammalian cell according to claim 22, wherein the at least one receptor that associates with DAP 10 is endogenous.
24. The mammalian cell according to claim 22, wherein the at least one receptor that associates with DAP 10 is over-expressed.
25. The mammalian cell according to claim 22, wherein the at least one receptor that associates with DAP 10 is exogenous.
26. The mammalian cell according to any one of claims 22-25, wherein the receptor is NKG2D.

27. The mammalian cell according to any one of claims 22-26, wherein the mammalian cell is an immune cell, preferably wherein said immune cell is a cytotoxic cell.
28. A method for activating an immune cell, comprising:
expressing the CAD polypeptide of claim 21 in the immune cell, wherein the immune cell expresses at least one receptor that associates with DAP 10; and
wherein the activating occurs responsive to the receptor engaging a corresponding target molecule.
29. The method according to claim 28, wherein the receptor is endogenous.
30. The method according to claim 28, wherein the receptor is exogenous.
31. The method according to claim 28, wherein the receptor is over-expressed.
32. The method according to any one of claims 28-31, wherein the receptor is NKG2D.
33. The method according to any one of claims 28-32, wherein the immune cell, or a plurality thereof, are to be introduced to a subject in need thereof; and
wherein the activating occurs in the subject.
34. Use of the mammalian cell, or a plurality thereof, according to any one of claims 22-27, in the preparation of a medicament for treating a subject with a condition for which the mammalian cell, or the plurality thereof, reduces at least one symptom or sign of said condition in the subject.
35. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a plurality of mammalian cells according to any one of claims 22-27.
36. The CAD polypeptide of claim 21 or the mammalian cell, or a plurality thereof, according to any one of claims 22-27 for use in therapy.