CLAIMS

1. An immunogenic composition comprising a mutant RAS peptide comprising a mutation at a position relative to G12 of wildtype RAS, wherein the mutant RAS peptide comprises an amino acid sequence that is at least 80% identical to an amino acid sequence selected from SEQ ID NOs: 1-16; and the mutation is selected from the group consisting of G12C, G12D, G12R and G12V mutation.

2. The composition of claim 1, wherein the mutant RAS peptide comprises 9 or 10 amino acid residues.

3. The composition of claim 1, wherein the mutant RAS peptide comprises an amino acid sequence selected from SEQ ID NOs:1-16.

4. An isolated nucleic acid molecule comprising a nucleic acid sequence encoding a mutant RAS peptide comprising a mutation at a position relative to G12 of wildtype RAS, wherein the mutant RAS peptide comprises an amino acid sequence that is at least 80% identical to an amino acid sequence selected from SEQ ID NOs: 1-16; and the mutation is selected from the group consisting of G12C, G12D, G12R and G12V mutation.

5. A cell modified to comprise or express a mutant RAS peptide comprising a mutation at a position relative to G12 of wildtype RAS, wherein the mutant RAS peptide comprises an amino acid sequence that is at least 80% identical to an amino acid sequence selected from SEQ ID NOs: 1-16; and the mutation is selected from the group consisting of G12C, G12D, G12R and G12V mutation.

6. The cell of claim 5, wherein the cell is an immune cell.

7. The cell of claim 6, wherein the immune cell is selected from the group consisting of an antigen presenting cell, B cell, dendritic cell, macrophage, Langerhans cell, T cell, NK cell, NK T cell.

8. A medicament for inducing an immune response in a subject, the medicament comprising the immunological composition of claim 1.

9. The medicament of claim 8, wherein the medicament further comprises a composition comprising or encoding a mutant RAS peptide comprising a mutation at a position relative to G12 of wildtype RAS, wherein the mutant RAS peptide binds to an identified HLA molecule of the subject.

10. The medicament of claim 10, wherein the subject has or is at risk for having a RAS-associated cancer.

11. The medicament of claim 12, wherein the cancer is selected from the group consisting of pancreatic cancer, pancreatic ductal adenocarcinoma (PDA), colon cancer, colorectal adenocarcinoma, myeloma, multiple myeloma, lung adenocarcinoma, melanoma, uterine cancer, thyroid cancer, acute myelogenous leukemia (AML), urothelial cancer, gastric adenocarcinoma and cervical adenocarcinoma, head and neck squamous cell carcinoma (SCC), Diffuse large B-cell lymphoma (DLBCL), esophageal adenocarcinoma, Chronic lymphocytic leukemia (CLL), lung SCC, small cell lung cancer (SCLC), renal papillary cancer, Hepatocellular carcinoma (HCC), breast cancer, cervical SCC, ovarian adenocarcinoma, adrenal cancer, prostate cancer, neuroblastoma, glioblastoma multiforme (GBM), medulloblastoma, Renal cell carcinoma (RCC), esophageal SCC, osteosarcoma, sarcoma, and small intestine neuroendocrine tumor (NET).

12. A medicament for inducing an immune response in a subject comprising a stimulated cell generated by contacting a cell with a composition comprising a mutant RAS peptide comprising a mutation at a position relative to G12 of wildtype RAS, wherein the mutant RAS peptide comprises an amino acid sequence that is at least 80% identical to an amino acid sequence selected from SEQ ID NOs: 1-16; and the mutation is selected from the group consisting of G12C, G12D, G12R and G12V mutation..

13. The medicament of claim 12, wherein the medicament comprises a stimulated T cell generated by contacting a naive T cell of the subject with an antigen presenting cell presenting the mutant RAS peptide.

14. The medicament of claim 12, wherein the cell is autologous to the subject.

15. The medicament of claim 13, wherein the T cell and antigen presenting cell are autologous to the subject.

16. A composition comprising a T-cell receptor (TCR) that specifically binds to a mutant RAS (mRAS) peptide in the context of an HLA molecule selected from the group consisting of: HLA-A*02:01, HLA-A*03:01, HLA-A*11:01, and HLA-B*07:02; wherein the TCR comprises
(a) an amino acid sequence that is at least 80% identical to the amino acid sequence of TRAV39 CDR1, TRAV12-1 CDR1, TRAV17 CDR1, TRAV19 CDR1, or TRAV4 CDR1

(b) ) an amino acid sequence that is at least 80% identical to the amino acid sequence of TRAV39 CDR2, TRAV12-1 CDR2, TRAV17 CDR2, TRAV19 CDR2, or TRAV4 CDR2;
(c) an amino acid sequence that is at least 80% identical to the amino acid sequence of TRAV39 CDR3, TRAV12-1 CDR3, TRAV17 CDR3, TRAV19 CDR3, or TRAV4 CDR3;
(d) an amino acid sequence that is at least 80% identical to the amino acid sequence of TRBV20-1 CDR1, TRBV28 CDR1, TRBV10-3 CDR1, TRBV11-2 CDR1, TRBV9 CDR1, or TRBV7-2 CDR1;
(e) an amino acid sequence that is at least 80% identical to the amino acid sequence of TRBV20-1 CDR2, TRBV28 CDR2, TRBV10-3 CDR2, TRBV11-2 CDR2, TRBV9 CDR2, or TRBV7-2 CDR2; and
(f) an amino acid sequence that is at least 80% identical to the amino acid sequence of TRBV20-1 CDR3, TRBV28 CDR3, TRBV10-3 CDR3, TRBV11-2 CDR3, TRBV9 CDR3, or TRBV7-2 CDR3.

17. The composition of claim 16, wherein the RAS peptide comprises a mutation at a position corresponding to G12 relative to wildtype RAS.

18. The composition of claim 17, wherein the mutation of the mRAS peptide corresponds to a mutation selected from the group consisting of G12C, G12D, G12R, and G12V; relative to wildtype RAS.

19. The composition of claim 16, wherein the TCR comprises an amino acid sequence that is at least 80% identical to the amino acid sequence of: TRAV39 CDR1, an amino acid sequence that is at least 80% identical to the amino acid sequence of: TRAV39 CDR2, an amino acid sequence that is at least 80% identical to the amino acid sequence of: TRAV39 CDR3, an amino acid sequence that is at least 80% identical to the amino acid sequence of: TRBV20-1 CDR1, an amino acid sequence that is at least 80% identical to the amino acid sequence of: TRBV20-1 CDR2, and an amino acid sequence that is at least 80% identical to the amino acid sequence of: TRBV20-1 CDR3.

20. The composition of claim 16, wherein the TCR comprises TRAV39 CDR1, TRAV39 CDR2, TRAV39 CDR3, TRBV20-1 CDR1, TRBV20-1 CDR2, and TRBV20-1 CDR3.

21. The composition of claim 16, wherein the TCR comprises an amino acid sequence that is at least 80% identical to the amino acid sequence of:: TRAV12-1 CDR1, an amino acid sequence that is at least 80% identical to

the amino acid sequence of: TRAV12-1 CDR2, an amino acid sequence that is at least 80% identical to the amino acid sequence of: TRAV12-1 CDR3, an amino acid sequence that is at least 80% identical to the amino acid sequence of: TRBV28 CDR1, an amino acid sequence that is at least 80% identical to the amino acid sequence of: TRBV28 CDR2, and an amino acid sequence that is at least 80% identical to the amino acid sequence of: TRBV28 CDR3.

22. The composition of claim 16, wherein the TCR comprises TRAV12-1 CDR1, TRAV12-1 CDR2, TRAV12-1 CDR3, TRBV28 CDR1, TRBV28 CDR2, and TRBV28 CDR3.

23. The composition of claim 16, wherein the TCR comprises an amino acid sequence that is at least 80% identical to the amino acid sequence of:: TRAV17 CDR1, an amino acid sequence that is at least 80% identical to the amino acid sequence of: TRAV17 CDR2, an amino acid sequence that is at least 80% identical to the amino acid sequence of: TRAV17 CDR3, an amino acid sequence that is at least 80% identical to the amino acid sequence of: TRBV10-3 CDR1, an amino acid sequence that is at least 80% identical to the amino acid sequence of: TRBV10-3 CDR2, and an amino acid sequence that is at least 80% identical to the amino acid sequence of: TRBV10-3 CDR3.

24. The composition of claim 16, wherein the TCR comprises TRAV17 CDR1, TRAV17 CDR2, TRAV17 CDR3, TRBV10-3 CDR1, TRBV10-3 CDR2, and TRBV10-3 CDR3.

25. The composition of claim 16, wherein the TCR comprises an amino acid sequence that is at least 80% identical to the amino acid sequence of: TRAV17 CDR1, an amino acid sequence that is at least 80% identical to the amino acid sequence of: TRAV17 CDR2, an amino acid sequence that is at least 80% identical to the amino acid sequence of: TRAV17 CDR3, an amino acid sequence that is at least 80% identical to the amino acid sequence of: TRBV11-2 CDR1, an amino acid sequence that is at least 80% identical to the amino acid sequence of: TRBV11-2 CDR2, and an amino acid sequence that is at least 80% identical to the amino acid sequence of: TRBV11-2 CDR3.

26. The composition of claim 16, wherein the TCR comprises TRAV17 CDR1, TRAV17 CDR2, TRAV17 CDR3, TRBV11-2 CDR1, TRBV11-2 CDR2, and TRBV11-2 CDR3.

27. The composition of claim 16, wherein the TCR comprises an amino acid sequence that is at least 80% identical to the amino acid sequence of: TRAV19 CDR1, an amino acid sequence that is at least 80% identical to the

amino acid sequence of: TRAV19 CDR2, an amino acid sequence that is at least 80% identical to the amino acid sequence of: TRAV19 CDR3, an amino acid sequence that is at least 80% identical to the amino acid sequence of: TRBV9 CDR1, an amino acid sequence that is at least 80% identical to the amino acid sequence of: TRBV9 CDR2, and an amino acid sequence that is at least 80% identical to the amino acid sequence of: TRBV9 CDR3.

28. The composition of claim 16, wherein the TCR comprises TRAV19 CDR1, TRAV19 CDR2, TRAV19 CDR3, TRBV9 CDR1, TRBV9 CDR2, and TRBV9 CDR3.

29. The composition of claim 16, wherein the TCR comprises an amino acid sequence that is at least 80% identical to the amino acid sequence of: TRAV4 CDR1, an amino acid sequence that is at least 80% identical to the amino acid sequence of: TRAV4 CDR2, an amino acid sequence that is at least 80% identical to the amino acid sequence of: TRAV4 CDR3, an amino acid sequence that is at least 80% identical to the amino acid sequence of: TRBV7-2 CDR1, an amino acid sequence that is at least 80% identical to the amino acid sequence of: TRBV7-2 CDR2, and an amino acid sequence that is at least 80% identical to the amino acid sequence of: TRBV7-2 CDR3.

30. The composition of claim 16, wherein the TCR comprises TRAV4 CDR1, TRAV4 CDR2, TRAV4 CDR3, TRBV7-2 CDR1, TRBV7-2 CDR2, and TRBV7-2 CDR3.

31. The composition of claim 16, wherein the composition comprises a fusion polypeptide comprising a TCR a chain and a TCR β chain.

32. The composition of claim 31, wherein the fusion polypeptide comprises a linker domain.

33. The composition of claim 32, wherein the linker domain is a cleavable linker domain.

34. A composition comprising an isolated nucleic acid molecule encoding a composition of any one of claims 16-33.

35. A cell modified to express a T-cell receptor (TCR) that specifically binds to a mutant RAS (mRAS) peptide in the context of an HLA molecule selected from the group consisting of: HLA-A*02:01, HLA-A*03:01, HLA-A*11:01, and HLA-B*07:02;

wherein the TCR Comprises

(a) an amino acid sequence that is at least 80% identical to the amino acid

sequence of TRAV39 CDR1, TRAV12-1 CDR1, TRAV17 CDR1, TRAV19 CDR1, or TRAV4 CDR1;

(b) an amino acid sequence that is at least 80% identical to the amino acid sequence of TRAV39 CDR2, TRAV12-1 CDR2, TRAV17 CDR2, TRAV19 CDR2, or TRAV4 CDR2;

(c) an amino acid sequence that is at least 80% identical to the amino acid sequence of TRAV39 CDR3, TRAV12-1 CDR3, TRAV17 CDR3, TRAV19 CDR3, or TRAV4 CDR3;

(d) an amino acid sequence that is at least 80% identical to the amino acid sequence of TRBV20-1 CDR1, TRBV28 CDR1, TRBV10-3 CDR1, TRBV11-2 CDR1, TRBV9 CDR1, or TRBV7-2 CDR1;

(e) an amino acid sequence that is at least 80% identical to the amino acid sequence of TRBV20-1 CDR2, TRBV28 CDR2, TRBV10-3 CDR2, TRBV11-2 CDR2, TRBV9 CDR2, or TRBV7-2 CDR2; and

(f) an amino acid sequence that is at least 80% identical to the amino acid sequence of TRBV20-1 CDR3, TRBV28 CDR3, TRBV10-3 CDR3, TRBV11-2 CDR3, TRBV9 CDR3, or TRBV7-2 CDR3.

36. The cell of claim 35, wherein the mRAS peptide comprises a mutation at a position corresponding to G12 relative to wildtype RAS.

37. The cell of claim 36, wherein the mutation of the mRAS peptide corresponds to a mutation selected from the group consisting of G12C, G12D, G12R, and G12V; relative to wildtype RAS.

38. The cell of claim 35, wherein the cell is modified to express a fusion polypeptide comprising a TCR alpha chain and a TCR beta chain.

39. The cell of claim 35, wherein the cell is genetically modified by introduction of an isolated nucleic acid molecule encoding a polypeptide comprising at least one of: a TCR alpha chain and a TCR beta chain.

40. The cell of claim 35, wherein the cell is an immune cell.

41. The cell of claim 40, wherein the immune cell is selected from the group consisting of a T cell, NK cell, and NK T cell.

42. The cell of claim 35, wherein the cell is autologous to a subject having a cancer associated with RAS.

43. The cell of claim 35, wherein the cell is autologous to a subject having a HLA type selected from the group consisting of: HLA-A*02:01, HLA-A*03:01, HLA-A*11:01, and HLA-B*07:02.

44. A medicament for treating a cancer associated with mRAS in a subject in need thereof, the medicament comprising the cell of any one of claims 35-43.

45. The medicament of claim 44, wherein the cancer associated with mRAS is selected from the group consisting of pancreatic cancer, pancreatic ductal adenocarcinoma (PDA), colon cancer, colorectal adenocarcinoma, myeloma, multiple myeloma, lung adenocarcinoma, melanoma, uterine cancer, thyroid cancer, acute myelogenous leukemia (AML), urothelial cancer, gastric adenocarcinoma and cervical adenocarcinoma, head and neck squamous cell carcinoma (SCC), Diffuse large B-cell lymphoma (DLBCL), esophageal adenocarcinoma, Chronic lymphocytic leukemia (CLL), lung SCC, small cell lung cancer (SCLC), renal papillary cancer, Hepatocellular carcinoma (HCC), breast cancer, cervical SCC, ovarian adenocarcinoma, adrenal cancer, prostate cancer, neuroblastoma, glioblastoma multiforme (GBM), medulloblastoma, Renal cell carcinoma (RCC), esophageal SCC, osteosarcoma, sarcoma, and small intestine neuroendocrine tumor (NET).

46. The medicament of claim 44, wherein the subject has an identified HLA type.

47. The medicament of claim 44, wherein the medicament comprises one or more cells of the subject that is isolated and modified to express the TCR.

48. The medicament of claim 44, wherein the medicament comprises one or more cells modified to express the TCR by contacting the one or more cells with an isolated nucleic acid molecule that encodes one or more of: a TCR alpha chain and a TCR beta chain.