CLAIMS

1. An anti-CTLA-4 antibody, wherein the antibody does not confer systemic T cell activation or preferential expansion of self-reactive T cells.

2. An anti-CTLA-4 antibody, wherein the antibody allows CTLA-4 to cycle back to a cell surface.

3. The anti-CTLA-4 antibody of claim 2, wherein the antibody binds to CTLA-4 with a higher affinity at pH 7 as compared to pH 5.5.

4. The anti-CTLA-4 antibody of claim 2, wherein the antibody binds to CTLA-4 with a higher affinity at pH 7 as compared to pH 4.5.

5. The anti-CTLA-4 antibody of any one of claims 2-4, wherein the antibody induces FcR-mediated T regulatory cell depletion in a tumor microenvironment.

6. The anti-CTLA-4 antibody of any one of claims 2-5, wherein the antibody does not confer systemic T cell activation or preferential expansion of self-reactive T cells.

7. The anti-CTLA-4 antibody of any of the preceding claims, wherein the antibody does not block binding of CTLA-4 to its B7 ligand.

8. The anti-CTLA-4 antibody of any one of the preceding claims, wherein the anti-CTLA-4 antibody has reduced affinity to soluble CTLA-4 compared to CTLA-4 located on the cell surface.

9. The anti-CTLA-4 antibody of any of the preceding claims, wherein the anti-CTLA-4 antibody is combined with an anti-PD-1 antibody or anti-PD-L1 antibody.

10. A method of identifying an anti-CTLA-4 antibody that induces lower levels of immunotherapy-related adverse events (irAE), comprising:

(a) providing cells comprising cell surface CTLA-4;

(b) contacting the cells of (b) with a candidate anti-CTLA-4 antibody;

(c) following a period of incubation, detecting the amount of cell surface CTLA-4;

(d) comparing the amount of cell surface CTLA-4 from step (c) to a threshold level, wherein the threshold level is the amount of cell surface CTLA-4 from cells that were contacted with a control anti-CTLA-4 antibody,

wherein a higher amount of cell surface CTLA-4 as compared to the threshold level identifies the candidate anti-CTLA-4 antibody as an anti-CTLA-4 antibody that induces lower levels of irAE.

11. The method of claim 10, wherein the control anti-CTLA-4 antibody is Ipilimumab or Tremelimumab.

12. The method of claim 10, wherein the cells of step (a) express human CTLA-4.

13. The method of claim 10, wherein the cell surface CTLA-4 is detectably labeled.

14. The method of claim 13, wherein the detectable label is a fluorescent tag.

15. The method of claim 14, wherein the fluorescent tag is orange fluorescent protein.

16. The method of claim 10, wherein the detecting of step (c) comprises measuring the amount of the detectable label of the cell surface CTLA-4 using a Western blot, immunohistochemistry, or flow cytometry.

17. The method of claim 10, wherein the incubation of step (c) comprises contacting the candidate anti-CTLA-4 antibody with a detectably labeled anti-IgG antibody, and measuring the amount of the detectable label of the detectably labeled anti-IgG antibody using a Western blot, immunohistochemistry or flow cytometry.

18. The method of claim 17, wherein the detectable label of the detectably labeled anti-IgG antibody comprises alex488.

19. The method of claim 10, wherein the cells are selected from the group consisting of 293T cells, Chinese Hamster Ovary cells, and T regulatory cells (Tregs).

20. An anti-CTLA-4 antibody that has higher binding affinity for CTLA-4 at a high pH of 6.5-7.5 as compared to a low pH of less than or equal to 6.

21. The antibody of claim 20, wherein the high pH is 7 and the low pH is 4.5.

22. The antibody of claim 20, wherein the high pH is 7 and the low pH is 5.5.

23. A method of screening for or designing an anti-CTLA-4 antibody for use in immunotherapy, wherein the anti-CTLA-4 antibody does not cause lysosomal CTLA-4 degradation.

24. The method of claim 23, comprising

(a) contacting the anti-CTLA-4 antibody with a CTLA-4 protein at a pH of 6.5-7.5, and quantifying the amount of anti-CTLA-4 antibody binding to the CTLA-4 protein;

(b) contacting the anti-CTLA-4 antibody with a CTLA-4 protein at a pH of 4.5-5.5, and quantifying the amount anti-CTLA-4 antibody binding to the CTLA-4 protein;

(c) comparing the amount of binding in (a) and (b),

wherein the anti-CTLA-4 antibody does not cause lysosomal CTLA-4 degradation if the amount of binding in (a) as compared to (b) is greater than or equal to a threshold level.

25. The method of claim 24, wherein the pH of (a) is 7.0, the pH of (b) is 5.5, and the threshold level is 3-fold.

26. The method of claim 24, wherein the pH of (a) is 7.0, the pH of (b) is 4.5, and the threshold level is 10-fold.

27. The method of any one of claims 24-26, wherein the amount of anti-CTLA-4 antibody binding is the amount of anti-CTLA-4 antibody required to achieve 50% maximal binding to the CTLA-4 protein.

28. The method of claim 23, wherein the anti-CTLA-4 antibody allows CTLA-4 that has been bound at a cell surface to recycle back to the cell surface after endocytosis.

29. Use of an anti-CTLA-4 antibody in the manufacture of a medicament for treating cancer, wherein the binding of the antibody to CTLA-4 is disrupted at an acidic pH corresponding to that found in endosomes and lysosomes.

30. The use of claim 29, wherein the anti-CTLA-4 antibody exhibits a reduction of at least 3-fold in its binding to CTLA-4 at pH 5.5 as compared to pH 7.0.

31. The use of claim 29, wherein the antibody exhibits a reduction of at least 10-fold in its binding to CTLA-4 at pH 4.5 as compared to pH 7.0.

32. The use of claim 29, wherein the anti-CTLA-4 antibody exhibits a greater reduction in binding to soluble CTLA-4 than to cell-surface-bound or immobilized CTLA-4, as compared to Ipilimumab or Tremelimumab.

33. An anti-CTLA-4 antibody identified, screened or designed according to any one of claims 10-19 and 23-28.

34. Use of the antibody of any one of claims 1-8, 20-22, and 33 in the manufacture of a medicament for treating cancer.

35. The use of claim 34, wherein the anti-CTLA-4 antibody is in combination with an anti-PD-1 or anti-PD-L1 antibody.