Claims

1. A method of reducing tumour immunosuppression, comprising:
administering to an individual in need thereof a conjugate comprising one or more carbon monoxide releasing groups and a tumour-selective ligand, and optionally administering a cancer immunotherapy.

2. The method of claim 1, comprising administering a cancer immunotherapy.

3. The method according to claim 1, wherein the cancer is an immunosuppressive cancer.

4. The method according to claim 3, wherein the immunosuppressive cancer is characterised by immune checkpoint protein mediated inhibition of T cell function.

5. The method according to claim 4, wherein the immune checkpoint protein is CTLA-4.

6. The method according to claim 4, wherein the immune checkpoint protein is PD-1.

7. The method according to claim 3, wherein the immunosuppressive cancer is characterised by the presence of T-cell inhibitory cells in tumour tissue of the individual.

8. The method according to claim 7, wherein the T-cell inhibitory cells are tumour-associated macrophages (TAMs).

9. The method according to any one of claims 1 to 8, wherein the carbon monoxide releasing groups are metal carbonyl groups.

10. The method according to claim 9, wherein the metal carbonyl groups are mono-, di-, tri-, tetra- or penta-carbonyl metal groups.

11. The method according to claim 9 or claim 10, wherein the carbon monoxide releasing group comprises a metal atom selected from ruthenium, molybdenum, cobalt, rhenium, and iron.

12. The method of claim 11, wherein the metal atom is ruthenium or molybdenum.

13. The method according to any one of claims 9 to 12, wherein the conjugate has the formula Ligand-[Metal(CO)n1]n_2 where n_1 is between 1 and 5 and n_2 is between 1 and 30.

14. The method according to any one of claims 9 to 13, wherein the carbon monoxide releasing groups are ruthenium carbonyl groups.

15. The method according to claim 14, wherein the conjugate has the formula Ligand-[Ru $(CO)_2$]n, where n is between 1 and 16.

16. The method according to claim 15, wherein the carbon monoxide releasing groups are $Ru^{II}(CO)_2$.

17. The method according to any one of claims 1 to 16, wherein the conjugate comprises two or more carbon monoxide releasing groups.

18. The method of claim 17, wherein the conjugate is a nanoparticle encapsulating the carbon-monoxide-releasing groups, with the tumour selective ligand conjugated to the surface of the nanoparticle.

19. The method of claim 18, wherein the nanoparticle comprises a polymeric or inorganic core or shell.

20. The method of claim 18 or 19, wherein the nanoparticle comprises a block co-polymer comprising PEG.

21. The method of claim 20, wherein the nanoparticle comprises PEG block copolymers, with tumour selective ligand conjugated to the PEG terminus.

22. The method of any one of claims 1 to 21, wherein the tumour selective ligand is a biopolymer, synthetic polymer, peptide, aptamer, or small molecule.

23. The method according to claim 22, wherein the tumour selective ligand is a protein.

24. The method according to claim 23, wherein the tumour selective ligand is a plasma protein.

25. The method of claim 24, wherein the tumour-selective ligand is an antibody, albumin, globulin, lipoprotein, or transferrin.

26. The method of claim 25, wherein the tumour-selective ligand is serum albumin or fragment thereof.

27. The method according to claim 26, wherein the plasma protein is human serum albumin.

28. The method according to claim 27, wherein the tumour-selective ligand comprises an antibody or antigen-binding portion thereof.

29. The method according to claim 28, wherein the antibody or antigen-binding portion thereof specifically binds a tumour antigen.

30. The method according to claim 28, wherein the antibody or antigen binding portion thereof specifically binds to PD-1 or CTLA4.

31. The method according to any one of claims 23 to 30, wherein the carbon monoxide releasing groups are attached to histidine residues in the protein by dative covalent bonds.

32. The method according to any one of claims 23 to 31 wherein the conjugate is produced by reacting the protein with a CO releasing molecule comprising one or more metal carbonyl groups, such that one or more histidine residues of the protein are metalated with the metal carbonyl groups.

33. The method according to claim 32 wherein the conjugate is produced by reacting the protein with CORM-3, such that one or more histidine residues of the protein are metalated with ruthenium dicarbonyl groups.

34. The method according to any one of claims 1 to 33, wherein the cancer is a solid cancer such as sarcoma, carcinoma, or lymphoma.

35. The method according to claim 34, wherein the cancer is skin cancer, melanoma, bladder cancer, brain cancer, breast cancer, uterus cancer, oral cancer, ovary cancer, prostate cancer, lung cancer, colorectal cancer, cervical cancer, liver cancer, head and neck cancer, oesophageal cancer, pancreas cancer, renal cancer, adrenal cancer, stomach cancer, testicular cancer, cancer of the gall bladder and biliary tracts, thyroid cancer, thymus cancer, and bone cancer.

36. The method according to claim 34 or claim 35, wherein the cancer is a primary tumour.

37. The method according to claim 34 or claim 35, wherein the cancer is metastatic.

38. The method according to any one of claims 1 to 37, wherein the conjugate is administered once or twice per week or once or twice per month.

39. The method according to any one of claims 1 to 38, wherein the conjugate is administered for at least four weeks.

40. The method according to any one of claims 1 to 39, wherein the CO releasing conjugate is administered intravenously.

41. The method according to any one of claims 1 to 40, wherein conjugate is administered to the individual in combination with cancer immunotherapy.

42. The method according to claim 41, wherein the cancer immunotherapy is selected from immune checkpoint inhibitor therapy, cytokine therapy, immune co-stimulatory therapy, and adoptive cell therapy.

43. The method according to claim 41 or 42, wherein the cancer immunotherapy is an immune checkpoint inhibitor selected from an anti-CTLA-4 antibody, an anti-PD-1 antibody, and an anti-PD-L1 antibody.

44. The method according to claim 43, wherein the immune checkpoint inhibitor is ipilimumab, tremelimumab, nivolumab, pembrolizumab, durvalumab, atezolizumab, and avelumab.

45. The method according to claim 41 or claim 42, wherein the cancer immunotherapy is an immune co-stimulatory therapy, which is optionally a CD28 agonist or an OX40 agonist.

46. The method according to claim 41 or claim 42, wherein the cancer immunotherapy is an adoptive cell therapy.

47. The method according to claim 46, wherein the cancer immunotherapy is T cell adoptive cell therapy.

48. The method according to claim 46 or claim 47, wherein the cancer immunotherapy is a chimeric antigen receptor (CAR) T cell therapy.

49. The method according to any one of claims 1 to 48, wherein the therapeutic regimen includes administration of the conjugate for one to four weeks before initiating an immunotherapy regimen.

50. The method according to any one of claims 1 to 49, wherein the therapeutic regimen includes administration of the conjugate for one or more weeks or months after the completion of a cancer immunotherapy regimen.

51. The method according to any one of claims 1 to 50, wherein the conjugate and immunotherapy are administered in a regimen that includes concomitant therapy.

52. The method according to any one of claims 1 to 51, wherein the patient was previously unresponsive to, only partially responsive to, or had become resistant to, an immunotherapy, which is optionally a checkpoint inhibitor therapy.

53. The method according to claim 52, wherein the patient is refractory to CTLA-4 or PD-1 blockade therapy.

54. The conjugate comprising one or more carbon monoxide releasing groups and a tumour-selective ligand for use in a method of treatment of an immunosuppressive cancer, a method of treatment of cancer, or a method of treatment of reducing tumour immunosuppression according to any one of claims 1 to 53.

55. Use of a conjugate comprising one or more carbon monoxide releasing groups attached to a tumour-selective ligand in the manufacture of a medicament for use in a method of treating an immunosuppressive cancer, a method of treatment of cancer, or a method of treatment of reducing tumour immunosuppression according to any one of claims 1 to 53.