Claims

1. An inhibitor of EGFR signalling, and an inhibitor of MyD88-dependent TLR/IL-R1 signalling, for use in the prevention or treatment of a neurodegenerative disease.

2. Use of an inhibitor of EGFR signalling, and an inhibitor of MyD88-dependent TLR/IL-R1 signalling, in the manufacture of a medicament for the prevention or treatment of a neurodegenerative disease.

3. The use according to claim 1 or 2, wherein the EGFR inhibitor inhibits EGFR signalling so as to inhibit microglial cell activation and/or formation of inclusions of TDP43.

4. The use according to any of claims 1 to 3, wherein the EGFR inhibitor inhibits formation of inclusions of TDP43 by inducing deacetylation of TDP43.

5. The use according to any of claims 1 to 4, wherein the EGFR inhibitor inhibits EGFR signalling by inhibiting EGFR tyrosine kinase activity.

6. The use according to any of claims 1 to 5, wherein the inhibitor of EGFR signalling is an inhibitor of EGFR tyrosine kinase.

7. The use according to claim 6, wherein the EGFR tyrosine kinase inhibitor is a small molecule tyrosine kinase inhibitor selected from a group consisting of gefitinib, erlotinib, brigatinib, lapatinib, afatinib, and icotinib.

8. The use according to any of claims 1 to 5, wherein the inhibitor of EGFR signalling inhibits binding of ligand to an extracellular binding domain of EGFR.

9. The use according to claim 8, wherein the inhibitor of EGFR signalling is a monoclonal antibody, or antigen-binding fragment thereof, that binds specifically to the extracellular binding domain of EGFR.

10. The use according to claim 9, wherein the monoclonal antibody is selected from a group consisting of cetuximab, panitumumab, zalutumumab, nimotuzumab, and matuzumab.

11. The use according to any of claims 1 to 10, wherein the inhibitor of MyD88-dependent TLR/IL-R1 signalling inhibits MyD88-dependent TLR/IL-R1 signalling so as to inhibit production of IL-1β and NFkB and/or to inhibit formation of inclusions of TDP43.

12. The use according to claim 11, wherein the inhibitor of MyD88-dependent TLR/IL-R1 signalling inhibits formation of inclusions of TDP43 by inhibiting phosphorylation of TDP43.

13. The use according to any of claims 1 to 12, wherein the inhibitor of MyD88-dependent TLR/IL-R1 signalling inhibits MyD88-dependent TLR/IL-R1 signalling by inhibiting IRAK1 and/or IRAK4.

14. The use according to claim 13, wherein the inhibitor of MyD88-dependent TLR/IL-R1 signalling is a small molecule inhibitor of IRAK1 and/or IRAK4.

15. The use according to claim 13 or 14, wherein the inhibitor of EGFR signalling and the inhibitor of MyD88-dependent TLR/IL-R1 signalling are selected from a group consisting of lestaurtinib, tamatinib, sunitinib, SU-14813, staurosporine, NVP-TAE684, KW-2449, crizotinib, gefitinib, AST-487, dovitinib, JNJ-28312141, fedratinib, afatinib, ruxolitinib, canertinib, alvocidib, bosutinib, imatinib, vandetanib, PHA-665752, BI-2536, neratinib, and tandutinib.

16. The use according to claim 13 or 14, wherein the inhibitor of MyD88-dependent TLR/IL-R1 signalling is gefitinib.

17. The use according to any of claims 1 to 16, wherein the inhibitor of EGFR signalling, and of MyD88-dependent TLR/IL-R1 signalling is gefitinib.

18. The use according to any of claims 1 to 17, wherein the inhibitor of EGFR signalling, and the inhibitor of MyD88-dependent TLR/IL-R1 signalling, are to be administered directly to a brain or spinal cord.

19. The use according to any of claims 1 to 17, which further includes a P-glycoprotein inhibitor.

20. The use according to any of claims 1 to 19, wherein the neurodegenerative disease is a motor neuron disease.

21. The use according to claim 20, wherein the motor neuron disease is ALS.

22. The use according to any of claims 1 to 21, wherein the neurodegenerative disease is a familial neurodegenerative disease.

23. The use according to claim 19, wherein the P-glycoprotein inhibitor is elacridar.

24. A pharmaceutical composition, which comprises an inhibitor of EGFR signalling, and an inhibitor of MyD88-dependent TLR/IL-R1 signalling, and a pharmaceutically acceptable carrier, excipient, or diluent, wherein the inhibitor of EGFR signalling, and the inhibitor of MyD88-dependent TLR/IL-R1 signalling are different compounds.

25. A combined preparation, which comprises: (a) an inhibitor of EGFR signalling; and (b) an inhibitor of MyD88-dependent TLR/IL-R1 signalling, wherein the inhibitor of EGFR signalling, and the inhibitor of MyD88-dependent TLR/IL-R1 signalling are different compounds.

26. The pharmaceutical composition according to claim 24, or the combined preparation according to claim 25, which further comprises a P-glycoprotein inhibitor.

27. The pharmaceutical composition, or the combined preparation according to claim 26, wherein the P-glycoprotein inhibitor is selected from a group consisting of cyclosporine A, ketoconazole, quinidine, ritonavir, verapamil, everolimus, and elacridar.

28. A composition, which comprises gefitinib, and a P-glycoprotein inhibitor.

29. A pharmaceutical composition, which comprises gefitinib, and a P-glycoprotein inhibitor, and a pharmaceutically acceptable carrier, excipient, or diluent.

30. A combined preparation, which comprises: (a) gefitinib; and (b) a P-glycoprotein inhibitor.

31. The composition according to claim 28, the pharmaceutical composition according to claim 29, or the combined preparation according to claim 30, wherein the P-glycoprotein inhibitor is selected from a group consisting of cyclosporine A, ketoconazole, quinidine, ritonavir, verapamil, everolimus, and elacridar.

32. The composition according to claim 28, the pharmaceutical composition according to claim 29, or the combined preparation according to claim 30, wherein the P-glycoprotein inhibitor is quinidine.

33. A pharmaceutical composition, which comprises an inhibitor of EGFR signalling, and an inhibitor of MyD88-dependent TLR/IL-R1 signalling, and a pharmaceutically acceptable carrier, excipient, or diluent, wherein the pharmaceutical composition is suitable for, or adapted for, administration directly to a CNS.

34. The pharmaceutical composition according to claim 33, which comprises one or more electrolytes present in endogenous CSF, wherein the one or more electrolytes is selected from sodium, potassium, calcium, magnesium, phosphorous, and chloride ions.

35. The pharmaceutical composition according to claim 34, which comprises a solution comprising 150mM sodium ion, 3mM potassium ion, 1.4mM calcium ion, 0.8mM magnesium ion, 1.0mM phosphorous ion, and 155mM chloride ion.

36. The pharmaceutical composition according to any of claims 33 to 35, wherein the inhibitor of EGFR signalling, and the inhibitor of MyD88-dependent TLR/IL-R1 signalling is gefitinib.

37. The composition, the pharmaceutical composition, or the combined preparation according to any of claims 28 to 36 for use in the prevention or treatment of a neurodegenerative disease.

38. Use of the composition, the pharmaceutical composition, or the combined preparation according to any of claims 28 to 36 in the manufacture of a medicament for the prevention or treatment of a neurodegenerative disease.

39. The use according to claim 37 or 38, wherein the neurodegenerative disease is a motor neuron disease.

40. The use according to claim 39, wherein the motor neuron disease is amyotrophic lateral sclerosis (ALS).

41. The use according to any of claims 37 to 40, wherein the neurodegenerative disease is a familial neurodegenerative disease.

Claims

1. Use of an inhibitor of EGFR signalling, and an inhibitor of MyD88-dependent TLR/IL-R1 signalling, in the manufacture of a medicament for the prevention or treatment of a neurodegenerative disease, wherein the inhibitor is gefitinib and the disease is amyotrophic lateral sclerosis (ALS).

2. The use according to claim 1, wherein the EGFR inhibitor inhibits EGFR signalling so as to inhibit microglial cell activation and/or formation of inclusions of TDP43.

3. The use according to claim 1 or 2, wherein the EGFR inhibitor inhibits formation of inclusions of TDP43 by inducing deacetylation of TDP43.

4. The use according to any of claims 1 to 3, wherein the EGFR inhibitor inhibits EGFR signalling by inhibiting EGFR tyrosine kinase activity.

5. The use according to any of claims 1 to 4, wherein the inhibitor of EGFR signalling is an inhibitor of EGFR tyrosine kinase.

6. The use according to any of claims 1 to 5, wherein the inhibitor of MyD88-dependent TLR/IL-R1 signalling inhibits MyD88-dependent TLR/IL-R1 signalling so as to inhibit production of IL-1β and NFkB and/or to inhibit formation of inclusions of TDP43.

7. The use according to claim 6, wherein the inhibitor of MyD88-dependent TLR/IL-R1 signalling inhibits formation of inclusions of TDP43 by inhibiting phosphorylation of TDP43.

8. The use according to any of claims 1 to 7, wherein the inhibitor of MyD88-dependent TLR/IL-R1 signalling inhibits MyD88-dependent TLR/IL-R1 signalling by inhibiting IRAK1 and/or IRAK4.

9. The use according to any of claims 1 to 8, wherein the inhibitor of EGFR signalling, and the inhibitor of MyD88-dependent TLR/IL-R1 signalling, are to be administered directly to a brain or spinal cord.

10. The use according to any of claims 1 to 8, which further includes a P-glycoprotein inhibitor.

11. The use according to claim 10, wherein the P-glycoprotein inhibitor is elacridar.

12. A composition, which comprises gefitinib, and a P-glycoprotein inhibitor, wherein the P-glycoprotein inhibitor is elacridar or quinidine.

13. A pharmaceutical composition, which comprises gefitinib, and a P-glycoprotein inhibitor, and a pharmaceutically acceptable carrier, excipient, or diluent, wherein the P-glycoprotein inhibitor is elacridar or quinidine.

14. A combined preparation, which comprises: (a) gefitinib; and (b) a P-glycoprotein inhibitor, the P-glycoprotein inhibitor is elacridar or quinidine.

15. A pharmaceutical composition, which comprises an inhibitor of EGFR signalling, and an inhibitor of MyD88-dependent TLR/IL-R1 signalling, and a pharmaceutically acceptable carrier, excipient, or diluent, wherein the pharmaceutical composition is suitable for, or adapted for, administration directly to a CNS, and wherein the inhibitor is gefitinib.

16. The pharmaceutical composition according to claim 15, which comprises one or more electrolytes present in endogenous CSF, wherein the one or more electrolytes is selected from sodium, potassium, calcium, magnesium, phosphorous, and chloride ions.

17. The pharmaceutical composition according to claim 16, which comprises a solution comprising 150mM sodium ion, 3mM potassium ion, 1.4mM calcium ion, 0.8mM magnesium ion, 1.0mM phosphorous ion, and 155mM chloride ion.

18. The pharmaceutical composition according to any of claims 15 to 17, wherein the inhibitor of EGFR signalling, and the inhibitor of MyD88-dependent TLR/IL-R1 signalling is gefitinib.

19. Use of the composition, the pharmaceutical composition, or the combined preparation according to any of claims 12 to 18 in the manufacture of a medicament for the prevention or treatment of a neurodegenerative disease.

20. The use according to claim 19, wherein the neurodegenerative disease is a motor neuron disease.

21. The use according to claim 20, wherein the motor neuron disease is amyotrophic lateral sclerosis (ALS).

22. The use according to any of claims 19 to 21, wherein the neurodegenerative disease is a familial neurodegenerative disease.