CLAIMS

1. Use of haptoglobin (Hp) in the preparation of a medicament for treating or preventing an adverse secondary neurological outcome in a subject following a haemorrhagic stroke.

~~2. A pharmaceutical composition for use in treating or preventing an adverse secondary neurological outcome in a subject following a haemorrhagic stroke, the composition comprising haptoglobin (Hp) and a pharmaceutically acceptable carrier.~~

~~3~~2. The use ~~or composition~~ of claim 1 ~~or claim 2~~, wherein the Hp is present in an amount of from 2 μM to 20 mM.

~~4~~3. The use ~~or composition~~ of ~~any one of the preceding~~ claim~~s~~ 1 or 2, wherein the Hp is present in an amount of from 2 μM to 300 μM, from 5 μM to 50 μM, or from 10 μM to 30 μM,

~~5~~4. The use ~~or composition~~ of any one of the preceding claims, wherein the Hp is selected from the group consisting of an Hp1-1 homodimer, an Hp1-2 multimer, an Hp2-2 multimer and a combination of any of the foregoing.

~~6~~5. The use ~~or composition~~ of claim ~~7~~4, comprising a Hp2-2 multimer.

~~7~~6. The use ~~or composition~~ of any one of the preceding claims, ~~wherein the method of treating or preventing an adverse secondary neurological outcome in a subject following a haemorrhagic stroke is accompanied by extravascular erythrolysis and release of cell-free haemoglobin (Hb) into a cerebral spinal fluid (CSF),~~ wherein ~~the method comprising exposing~~ the CSF of ~~a~~the subject in need thereof is to be exposed to a therapeutically effective amount of haptoglobin (Hp) ~~and~~ for a period of time sufficient to allow the Hp to form a complex with, and thereby neutralise, the cell-free Hb.

~~8~~7. The use ~~or composition~~ of any one of the preceding claims, wherein the haemorrhagic stroke is a spontaneous haemorrhage or a traumatic haemorrhage.

~~9~~8. The use ~~or composition~~ of any one of the preceding claims, wherein the haemorrhagic stroke is an intraventricular haemorrhage or a subarachnoid haemorrhage.

~~10~~9. The use ~~or composition~~ of claim ~~9~~8, wherein the subarachnoid haemorrhage is an aneurysmal subarachnoid haemorrhage.

1~~1~~0. The use ~~or composition~~ of any one of the preceding claims, wherein the adverse secondary neurological outcome is selected from the group consisting of a delayed ischaemic neurological deficit (DIND), delayed cerebral ischaemia (DCI), neurotoxicity, inflammation, nitric oxide depletion, oxidative tissue injury, cerebral vasospasm, cerebral vasoreactivity and oedema.

1~~2~~1. The use ~~or composition~~ of claim 1~~1~~0, wherein the adverse secondary neurological outcome is a cerebral vasospasm.

1~~3~~2. The use ~~or composition~~ of claim 1~~1~~0, wherein the adverse secondary neurological outcome is a delayed ischaemic neurological deficit.

1~~4~~3. The use ~~or composition~~ of claim 1~~1~~0, wherein the adverse secondary neurological outcome is delayed cerebral ischaemia.

1~~5~~4. The use ~~or composition~~ of any one of the preceding claims, wherein the adverse secondary neurological outcome is an adverse secondary neurological outcome within the brain parenchyma.

1~~6~~5. The use ~~or composition~~ of any one of the preceding claims ~~9~~6 to 1~~5~~4, wherein ~~comprising exposing~~ the CSF of the subject is to be exposed to the Hp, or the functional analogue thereof, within about 21 days after onset of the haemorrhage.

1~~7~~6. The use ~~or composition~~ of claim 1~~6~~5, ~~comprising exposing~~wherein the CSF of the subject is to be exposed to the Hp from 2 days to 4 days after onset of the haemorrhage and/or from 5 days to 14 days after onset of the haemorrhage.

1~~8~~7. The use ~~or composition~~ of any one of the preceding claims, ~~comprising the~~wherein the Hp is to be intracranially administered to the subject.

1~~9~~8. The use ~~or composition~~ of any one of ~~the preceding~~ claims 1 to 16, wherein the Hp is to be intrathecally administered to the subject.

2019. The use or composition of claim 198, wherein the Hp is to be intrathecally administered into the spinal canal.

210. The use or composition of claim 198, wherein the Hp is to be intrathecally administered into the subarachnoid space.

221. The use or composition of any one of the preceding claims 1 to 16, wherein the Hp is to be intracerebroventricularly administered to the subject.

232. The use or composition of any one of claims 187 to 221, wherein the period of time to which the CSF is to be exposed to the therapeutically effective amount of Hp is at least about 2 minutes.

243. The use or composition of claim 232, wherein the period of time to which the CSF is to be exposed to the therapeutically effective amount of Hp is from 2 minutes to 45 minutes.

254. The use or composition of claim 232, wherein the period of time to which the CSF is to be exposed to the therapeutically effective amount of Hp is from 2 minutes to 20 minutes or from 4 minutes to 10 minutes.

265. The use or composition of any one of claims 16 to 254, wherein the therapeutically effective amount of Hp is at least an equimolar amount to the concentration of cell-free Hb in the CSF of the subject following the haemorrhage.

276. The use or composition of claim 265, further comprisingwherein (i) obtaining a CSF sample from the subject following the haemorrhage and prior to exposing the CSF to the Hp; (ii) measuring the amount of cell-free Hb in thean isolated CSF sample following haemorrhage from the subject is measuredobtained in step (i); and (iii)to determineing the at least equimolar amount of Hp based on the concentration of cell-free Hb from step (ii).

287. The use or composition of any one of claims 7 to 276, further comprising removing Hp:cell-free Hb complexes formed in the CSF.

2~~9~~8. The use ~~or composition~~ of any one of claims 7 to ~~28~~ 27, wherein ~~comprising exposing~~ the CSF is to be exposed to the therapeutically effective amount of Hp extracorporeally.

~~30~~29. The use ~~or composition~~ of claim 2~~9~~8, comprising:

~~(i) obtaining sample of CSF from the CSF compartment of the subject following the haemorrhage;~~

(i~~i~~) adding to ~~the~~an isolated CSF sample from the CSG compartment ~~of s~~the~~p (i)~~subject Hp to obtain an Hp-enriched CSF sample;

(ii~~i~~) wherein the Hp-enriched CSF sample is to be administered to the subject, thereby exposing the CSF compartment of the subject to a therapeutically effective amount of Hp for a period of time sufficient to allow the Hp to form a complex with cell-free Hb in the CSF compartment of the subject; and

(i~~v~~ii) and (ii) and (iii) are to be optionally repeat~~ed~~ing ~~steps (i) to (iii)~~.

~~3~~10. The use ~~or composition~~ of claim 2~~9~~8, ~~comprising:~~wherein

~~(i) a volume of CSF is to be removed from the CSF compartment of the subject following the haemorrhage;~~

~~(ii) providing an artificial CSF comprising Hp;~~

(i~~i~~i) ~~the~~an artificial CSF ~~of (ii)~~comprising Hp is to be administered to replace a volume of CSF of the subject following haemorrhage, thereby exposing the CSF compartment of the subject to a therapeutically effective amount of Hp for a period of time sufficient to allow the Hp to form a complex with cell-free Hb in the CSF compartment of the subject; and

(i~~v~~i) (i) is optionally to be repeat~~ed~~ing ~~steps (i) to (iii)~~.

~~3~~21. The use ~~or composition~~ of claim 2~~9~~8, comprising:

~~(i) obtaining CSF from the subject following the haemorrhage;~~

(i~~i~~) exposing ~~the~~ isolated CSF sample following haemorrhage from ~~s~~the~~p (i)~~subject to ~~the~~ Hp under conditions to allow the Hp, or the functional analogue thereof, to form a complex with cell-free Hb in the CSF;

(ii~~i~~) extracting the Hp:cell-free Hb complexes from the CSF following step (ii) to obtain an Hb-diminished CSF that has a lower amount of cell-free Hb when compared to the CSF from step (i);

(i~~v~~ii) optionally repeating steps (i~~i~~) and (ii~~i~~) to obtain an Hb-diminished CSF that is substantially free of cell-free Hb; and wherein

(iv) the Hb-diminished CSF ~~obtained~~ from ~~step~~ (ii~~i~~) or ~~step~~ (i~~v~~ii) is to be administered to the CSF compartment of the subject.

3~~3~~2. The use ~~or composition~~ of claim 3~~2~~1, further comprising adding to the Hb-diminished CSF prior to step (vi) a therapeutically effective amount of Hp.

3~~4~~3. The use ~~or composition~~ of claim 3~~2~~1 or claim 3~~3~~2, wherein the Hp is immobilised on a substrate.

3~~5~~4. The use ~~or composition~~ of claim 3~~4~~3, wherein the substrate is an affinity chromatography resin.

3~~6~~5. The use ~~or composition~~ of claim 3~~5~~4, wherein step (ii) comprises passing the CSF from step (i) through an affinity chromatography resin under conditions that allow the cell-free Hb in the CSF to bind to the resin; wherein step (iii) comprises eluting the CSF from the resin following step (ii); and wherein step (iv) comprising recovering the eluted CSF.

3~~7~~6. The use ~~or composition~~ of any one of claims 3~~2~~1 to 3~~6~~5, optionally comprising washing the CSF compartment following step (i) with a wash solution.

3~~8~~7. The use ~~or composition~~ of claim 3~~7~~6, wherein the wash solution is an artificial CSF.

3~~9~~8. The use ~~or composition~~ of claim 3~~1~~0 or claim 3~~8~~7, wherein the artificial CSF comprises NaCl, KCl, KH_2PO_4, $NaHCO_3$, $MgCl_6H_20$, $CaCl_2H_2O$ and glucose.

~~40~~39. The use ~~or composition~~ of any one of claims 37 to 39, wherein the wash solution comprises Hp.

4~~1~~0. The use ~~or composition~~ of claim ~~40~~39, wherein the wash solution comprises from 2 µM to 20 mM Hp or from 2 µM to 300 µM Hp.

4~~2~~1. The use ~~or composition~~ of any one of claims ~~7~~6 to 4~~1~~0, ~~comprising~~wherein:

(i) the CSF is to be removed from the subject following the haemorrhage;

(ii) the CSF compartment of the subject following ~~step (i)~~ is to be rinsed with a wash solution comprising a therapeutically effective amount of Hp;

(iii) optionally repeating ~~step~~ (ii); and

(iv) an artificial CSF is to be administer~~ed~~ing to the CSF compartment of the subject, following ~~step~~ (ii) or ~~step~~ (iii).

4~~3~~2. The use ~~or composition~~ of claim 4~~2~~1, wherein the artificial CSF comprises NaCl, KCl, KH_2PO_4, $NaHCO_3$, $MgCl_6H_20$, $CaCl_2H_2O$ and glucose.

4~~4~~3. The use ~~or composition~~ of claim 4~~2~~1 or claim 4~~3~~2, wherein the artificial CSF comprises Hp.

4~~5~~4. The use ~~or composition~~ of claim 4~~4~~3, wherein the artificial CSF comprises from 2 µM to 20 mM Hp or from 2 µM to 300 µM Hp.

4~~6~~5. The use ~~or composition~~ of any one of claims 1 to 4~~5~~4, wherein the Hp is selected from the group consisting of an Hp1-1 homodimer, an Hp1-2 multimer, an Hp2-2 multimer and a combination of any of the foregoing.

4~~7~~6. The use ~~or composition~~ of claim 4~~6~~5, wherein the Hp comprises an Hp2-2 multimer.

4~~8~~7. The use ~~or composition~~ of any one of claims 1 to 4~~7~~6, wherein the Hp is a recombinant protein.

4~~9~~8. The use ~~or composition~~ of any one of claims 1 to 4~~7~~6, wherein the Hp is plasma derived.

~~50~~49. The use ~~or composition~~ of any one of claims 1 to 4~~9~~8, further comprising a second agent for treating or preventing an adverse secondary neurological outcome following an intraventricular haemorrhage to be administered to the subject.

5~~1~~0. The use ~~or composition~~ of claim ~~50~~49, wherein the second agent is a vasodilator.

5~~2~~1. The use ~~or composition~~ of claim ~~50~~49 or claim 5~~1~~0, wherein the second agent is selected from the group consisting of a sydnone and sodium nitroprusside.

5~~3~~2. An artificial cerebral spinal fluid (CSF) comprising Hp.

543. The artificial CSF of claim 532, wherein the Hp is present in an amount of from 2 μM to 20 mM, from 5 μM to 300 μM, from 5 μM to 50 μM or from 10 μM to 30 μM.

554. The artificial CSF ofany one of claims 532 tor 543, wherein the Hp is selected from the group consisting of an Hp1-1 homodimer, an Hp1-2 multimer, an Hp2-2 multimer and a combination of any of the foregoing.

565. The artificial CSF of claim 545, wherein the Hp comprisesing an Hp2-2 multimer.

576. The artificial CSF of any one of claims 532 to 565, wherein the Hp is a recombinant protein.

587. The artificial CSF of any one of claims 5352 to 57 56, wherein the Hp is plasma derived.

598. A kit comprising the artificial CSF of any one of claims 532 to 587 or the composition of any one of claims 2 to 52.