BLOOD BRAIN BARRIER SHUTTLE

The present invention relates to a blood brain barrier shuttle that binds receptors on the blood brain barrier (R/BBB) and methods of using the same.

BACKGROUND

Brain penetration of neurological disorder drugs such as e.g. large biotherapeutic drugs or small molecule drugs having a low brain penetration, is strictly limited by the extensive and impermeable blood-brain barrier (BBB) together with the other cell component in the neurovascular unit (NVU). Many strategies to overcome this obstacle have been tested and one is to utilize transcytosis pathways mediated by endogenous receptors expressed on the brain capillary endothelium. Recombinant proteins such as monoclonal antibodies or peptides have been designed against these receptors to enable receptor-mediated delivery of biotherapeutics to the brain. However, strategies to maximize brain uptake while minimizing miss-sorting within the brain endothelial cells (BECs), and the extent of accumulation within certain organelles (especially organelles that leads to degradation of the biotherapeutic) in BECs, remain unexplored.

Monoclonal antibodies and other biotherapeutics have huge therapeutic potential for treatment of pathology in the central nervous system (CNS). However, their route into the brain is prevented by BBB. Previous studies have illustrated that a very small percentage (approximately 0.1%) of an IgG injected in the bloodstream are able to penetrate into the CNS compartment (Felgenhauer, Klin. Wschr. 52: 1158-1164 (1974)). This will certainly limit any pharmacological effect due to the low concentration within CNS of the antibody.

Therefore, there is a need for delivery systems of neurological disorder drugs across the BBB to shuttle the drugs into the brain efficiently.

SUMMARY

The present disclosure provides a blood brain barrier shuttle comprising a brain effector entity, a linker and one monovalent binding entity which binds to a blood brain barrier receptor, wherein the linker couples the effector entity to the monovalent binding entity which binds to the blood brain barrier receptor. In a first aspect, the present disclosure provides a blood brain barrier shuttle comprising a brain effector entity, a linker and one monovalent binding entity which binds to a transferrin receptor, wherein the linker couples the effector entity to the monovalent binding entity which binds to the transferrin receptor, wherein the monovalent binding entity which binds to the transferrin receptor comprises one scFab directed to the transferrin receptor recognizing an epitope in the transferrin receptor comprised within the amino acid sequence of Seq. Id. No. 14, 15 or 16.

Claims

1. A blood brain barrier shuttle comprising a brain effector entity, a linker and one monovalent binding entity which binds to a transferrin receptor, wherein the linker couples the effector entity to the monovalent binding entity which binds to the transferrin receptor, wherein the monovalent binding entity which binds to the transferrin receptor comprises one scFab directed to the transferrin receptor recognizing an epitope in the transferrin receptor comprised within the amino acid sequence of Seq. Id. No. 14, 15 or 16.

2. The blood brain barrier shuttle of claim 1, wherein the monovalent binding entity which binds to the transferrin receptor is selected from the group consisting of proteins, polypeptides and peptides.

~~3. The blood brain barrier shuttle of claim 1 or 2, wherein the monovalent binding entity which binds to the transferrin receptor comprises a molecule selected from the group consisting of a blood brain barrier receptor ligand, scFv, Fv, scFab, VHH, preferably a scFab.~~

~~4. The blood brain barrier shuttle of any of claims 1 to 3, wherein the monovalent binding entity which binds to the transferrin receptor comprises one scFab directed to the transferrin receptor, preferably a scFab recognizing an epitope in the transferrin receptor comprised within the amino acid sequence of Seq. Id. No. 14, 15 or 16.~~

~~5~~3. The blood brain barrier shuttle of claims 1 or ~~4~~2, wherein the brain effector entity is selected from the group consisting of neurological disorder drugs, neurotrophic factors, growth factors, enzymes, cytotoxic agents, antibodies directed to a brain target, monoclonal antibodies directed to a brain target, peptides directed to a brain target.

~~6~~4. The blood brain barrier shuttle of claim ~~5~~3, wherein the brain target is selected from the group consisting of β-secretase 1, Aβ, epidermal growth factor, epidermal growth factor receptor 2, Tau, phosphorylated Tau, apolipoprotein E4, alpha synuclein, oligomeric fragments of alpha synuclein, CD20, huntingtin, prion protein, leucine rich repeat kinase 2, parkin, presenilin 2, gamma secretase, death receptor 6, amyloid precursor protein, p75 neurotrophin receptor and caspase 6.

~~7~~5. The blood brain barrier shuttle of any of claims 1 to ~~6~~4, wherein the brain effector entity is selected from the group consisting of proteins, polypeptides and peptides.

~~8~~6. The blood brain barrier shuttle of claim ~~7~~5, wherein the monovalent binding entity which binds to the transferrin receptor is coupled to the C-terminal end of the brain effector entity by the linker.

~~9~~7. The blood brain barrier shuttle of any of claims 1 to ~~8~~6, wherein the brain effector entity comprises a full length antibody directed to a brain target, preferably a full length IgG.

8. The blood brain barrier shuttle of claim 7, wherein the full length antibody is a full length IgG antibody.

~~10~~9. The blood brain barrier shuttle of claim ~~9~~8 comprising the full length IgG antibody as brain effector entity, the linker and one scFab as the monovalent binding entity which binds the transferrin receptor, wherein the scFab is coupled by the linker to the C-terminal end of the Fc part of one of the heavy chains of the IgG antibody.

~~11~~10. The blood brain barrier shuttle of any one of claims ~~9~~7 to ~~9 or 10~~, wherein the effector entity is a full length antibody directed to Aβ.

~~12~~11. The blood brain barrier shuttle of claim ~~11~~10, wherein the antibody directed to Aβ comprises (a) H-CDR1 comprising the amino acid sequence of Seq. Id. No. 5, (b) H-CDR2 comprising the amino acid sequence of Seq. Id. No. 6, (c) H-CDR3 comprising the amino acid sequence of Seq. Id. No. 7, (d) L-CDR1 comprising the amino acid sequence of Seq. Id. No. 8, (e) L-CDR2 comprising the amino acid sequence of Seq. Id. No. 9 and (f) L-CDR3 comprising the amino acid sequence of Seq. Id. No. 10.

~~13~~12. The blood brain barrier shuttle of claim ~~12~~11, wherein the antibody directed to Abeta comprises a V_H domain comprising the amino acid sequence of Seq. Id. No. 11 and a V_L domain comprising the amino acid sequence of Seq. Id. No. 12.

~~14~~13. The blood brain barrier shuttle of any one of claims ~~9~~7 to ~~9or 10~~, wherein the effector entity is a full length antibody directed to phosphorylated Tau and the monovalent binding entity is one scFab directed to the transferrin receptor.

~~15~~14. The blood brain barrier shuttle of any one of claims ~~9~~7 to ~~9or 10~~, wherein the effector entity is a full length antibody directed to alpha synuclein and the monovalent binding entity is one scFab directed to the transferrin receptor.

~~16~~15. The blood brain barrier shuttle of any of claims 1 to ~~15~~14, wherein the linker is a peptide linker.

16. The blood brain barrier shuttle of claim 15, wherein the linker is ~~, preferably~~ a peptide having ~~which is~~ an amino acid sequence with a length of at least 20 amino acids.

17. The blood brain barrier shuttle of claim 16, wherein the peptide has an amino acid sequence ~~, more preferably~~ with a length of 25 to 50 amino acids.

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~~17~~18. The blood brain barrier shuttle of any of claims 1 to ~~64~~, wherein the monovalent binding entity which binds to the transferrin receptor comprises a CH2-CH3 Ig entity and one scFab which binds to the transferrin receptor, wherein the scFab is coupled to a C-terminal end of the CH2-CH3 Ig entity by a second linker.

~~18~~19. The blood brain barrier shuttle of claim ~~17~~18 comprising the brain effector entity, the linker, the CH2-CH3 Ig domain, the second linker and one scFab which binds to the transferrin receptor, wherein the brain effector entity is coupled by the first linker to a N-terminal end of the CH2-CH3 Ig domain and the scFab is coupled to a C-terminal end of the CH2-CH3 Ig domain by the second linker.

~~19~~20. The blood brain barrier shuttle of claims ~~17~~ 18 or ~~18~~19, wherein the CH2-CH3 Ig entity is a CH2-CH3 IgG entity.

~~20~~21. A fusion protein to transport a brain effector entity across the blood brain barrier comprising a CH2-CH3 Ig entity, a linker and one scFab directed to a transferrin receptor, wherein the scFab is coupled to a C-terminal end of the CH2-CH3 Ig entity by the linker.

~~21~~22. The fusion protein to transport the brain effector entity across the blood brain barrier of claim ~~20~~21, wherein the brain effector entity is selected from the group consisting of neurological disorder drugs, neurotrophic factors, growth factors, enzymes, cytotoxic agents, antibody fragments or peptides directed to a brain target selected from the group consisting of scFv, Fv, scFab, Fab, VHH, $F(ab')_2$.

~~22~~23. The fusion protein to transport the brain effector entity across the blood brain barrier of claims ~~20~~21 or 22~~21~~, wherein the scFab directed to the transferrin receptor is a scFab directed to the transferrin receptor, preferably a scFab recognizing an epitope in the transferrin receptor comprised within the amino acid sequence of Seq. Id. No. 14, 15 or 16.

~~23~~24. The fusion protein to transport the brain effector entity across the blood brain barrier of any of claims ~~20-~~21 to ~~22~~23, wherein the linker is peptide linker.

~~24~~25. The fusion protein of any of claims ~~20~~21 to ~~23~~24, wherein the CH2-CH3 Ig entity is a CH2-CH3 IgG entity.

~~25~~26. A conjugate comprising a fusion protein to transport a brain effector entity across the blood brain barrier of any of claims ~~20-~~21 to ~~24~~25 and a brain effector entity coupled to a N-terminal end of the CH2-CH3 Ig entity of the fusion protein by a linker.

~~26~~27. The conjugate of claim ~~25~~26, wherein the brain effector entity is selected from the group consisting of proteins, polypeptides and peptides.

~~27~~28. The conjugate of claim ~~26~~26, wherein a C-terminal end of the effector entity is coupled to the N-terminal end of the CH2-CH3 Ig entity by the linker.