Blood brain barrier shuttle

FIELD OF THE INVENTION

The present invention concerns the fields of molecular medicine and targeted delivery of therapeutic or diagnostic agents. More specifically, the present invention relates to peptides that target the cerebrospinal fluid (CSF) and the brain of an organism.

BACKGROUND

Brain penetration and/or CSF 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) or blood-CSF barrier BCSFB (BCSFB) together with the other cell component of 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 and diagnostics 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 the 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. The cerebrospinal fluid (CSF) is in direct contact with the neurons in the CNS.

Therefore, there is a need for delivery systems of neurological disorder drugs that target the brain of an organism.

SUMMARY

The present disclosure provides a blood brain barrier shuttle comprising a brain effector entity and a brain targeting peptide comprising a three amino acid peptide motif

selected from the group consisting of: Phe-Lys-Leu (FKL), Arg-Gly-Leu (RGL), Ser-Arg-Gly (SRG), Tyr-Val-Leu (YVL), Trp-Gly-Phe (WGF), Val-Leu-His (VLH), Leu-Tyr-Val (LYV), Leu-Trp-Gly (LWG), Leu-His-Ser (LHS), His-Ser-Arg (HSR), Gly-Leu-Trp (GLW), Gly-Phe-Lys (GFK), Arg-Leu-Ser (RLS), Gly-Ser-Val (GSV), Ser-Val-Ser (SVS), Leu-Gly-Ser (LGS), Val-Arg-Phe (VRF), Ser-Asn-Thr (SNT), Arg-Phe-Arg (RFR), Asn-Thr-Arg (NTR), Leu-Ser-Asn (LSN), Gly-Phe-Val (GFV), Phe-Val-Arg (FVR), Phe-Arg-Leu (FRL), Trp-Arg-Val (WRV), Phe-Ser-Leu (FSL), Val-Phe-Ser (VFS), Val-Ala-Trp (VAW), Ser-Leu-Phe (SLF), Arg-Val-Phe (RVF), Leu-Phe-Trp (LFW), Lys-Val-Ala (KVA), Phe-Trp-Lys (FWK), Ala-Trp-Arg (AWR), Val-His-Gly (VHG), Ser-Val-His (SVH), His-Gly-Val (HGV), Arg-Val-Cys (RVC), Arg-Pro-Gln (RPQ), Gln-Lys-Ile (QKI), Pro-Gln-Lys (PQK), Asn-Gly-Ala (NGA), Lys-Ile-Asn (KIN), Ile-Asn-Gly (ING), Gly-Arg-Pro (GRP), Gly-Ala-Arg (GAR), Ala-Arg-Val (ARV), Leu-Ser-Gly (LSG), Val-Asp-Ser (VDS), Ser-Val-Asp (SVD).

In a first aspect, there is provided a blood brain barrier shuttle comprising a brain effector entity and a brain targeting peptide comprising a three amino acid motif, wherein the brain targeting peptide comprising the three amino acid peptide motif is selected from the group consisting of Seq. Id. No. 1, 6 and 8.

In a particular embodiment of the blood brain barrier shuttle, the brain targeting peptide comprising a three amino acid peptide motif comprises between 1 – 25 three amino acid peptide motifs, in particular 1 – 15, more particular 1 – 10, even more particular 1 -5 three amino acid peptide motifs.

In a particular embodiment of the blood brain barrier shuttle, the brain shuttle comprises the brain effector entity, a linker and the brain targeting peptide comprising a three amino acid peptide motif, wherein the linker couples the effector entity to the brain targeting peptide comprising a three amino acid peptide motif.

In a particular embodiment of the blood brain barrier shuttle, the brain targeting peptide comprising a three amino acid peptide motif is selected from the group consisting of Seq. Id. No. 1 to 36, preferably Seq. Id. No. 1, 6 and 8.

In a particular embodiment of the blood brain barrier shuttle, 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.

In a particular embodiment of the blood brain barrier shuttle, 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.

In a particular embodiment of the blood brain barrier shuttle, the brain effector entity is selected from the group consisting of proteins, polypeptides and peptides.

In a particular embodiment of the blood brain barrier shuttle, the brain effector entity comprises a full length antibody directed to a brain target, preferably a full length IgG.

In a particular embodiment of the blood brain barrier shuttle, the effector entity is a full length antibody directed to Aβ.

In a particular embodiment of the blood brain barrier shuttle, the effector entity is a full length antibody directed to phosphorylated Tau.

In a particular embodiment of the blood brain barrier shuttle, the effector entity is a full length antibody directed to alpha synuclein.

In a second aspect, the present disclosure provides a pharmaceutical formulation comprising the blood brain barrier shuttle of the present disclosure and a pharmaceutical carrier.

Furthermore, the present disclosure provides the use of the brain shuttle as a medicament, in particular the use of the brain shuttle for the treatment of a neurodegenerative disorder, in particular Alzheimer's disease and for the treatment of a neuroinflammatory disorder in particular Multiple Sclerosis. In a third aspect, the present disclosure provides use of the blood brain shuttle of the present disclosure for use as medicament.

In a fourth aspect, the present disclosure provides the blood brain barrier shuttle of the present disclosure to transport the brain effector entity across the blood brain barrier.

The disclosure includes a BBB shuttle comprising a brain targeting peptide that is covalently coupled to the agent to be delivered. The agent may be a drug, a chemotherapeutic agent, a radioisotope, a pro-apoptosis agent, an anti-angiogenic agent, a hormone, an enzyme, a cytokine, a growth factor, a cytotoxic agent, a peptide, a protein, an antibiotic, an antibody, a Fab fragment of an antibody, an smaller fragment of an antibody, an imaging agent, survival factor, an anti-apoptotic agent, a hormone antagonist or an antigen. In a further embodiment of the disclosure, an anti-angiogenic agent may be selected from the group consisting of thrombospondin, angiostatin 5, pigment epithelium-derived factor, angiotensin, laminin peptides, fibronectin peptides, plasminogen activator inhibitors, tissue metalloproteinase inhibitors, interferons, interleukin 12, platelet factor 4, IP-10, Gro-B, thrombospondin,

CLAIMS

1. A blood brain barrier shuttle comprising a brain effector entity and a brain targeting peptide comprising a three amino acid motif, wherein the brain targeting peptide comprising the three amino acid peptide motif is selected from the group consisting of Seq. Id. No. 1, 6 and 8.

2. The blood brain barrier shuttle of claim 1 comprising the brain effector entity, a linker and the brain targeting peptide selected from the group consisting of Seq. Id. No. 1, 6 and 8, wherein the linker couples the effector entity to the brain targeting peptide selected from the group consisting of Seq. Id. No. 1, 6 and 8.

3. The blood brain barrier shuttle of claim 1 or 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.

4. The blood brain barrier shuttle of claims 1 to 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.

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

6. The blood brain barrier shuttle of claims 1 to 5, wherein the brain effector entity comprises a full length antibody directed to a brain target, preferably a full length IgG.

7. The blood brain barrier shuttle of claim 6, wherein the effector entity is a full length antibody directed to Aβ.

8. The blood brain barrier shuttle of claim 6, wherein the effector entity is a full length antibody directed to phosphorylated Tau.

9. The blood brain barrier shuttle of claim 6, wherein the effector entity is a full length antibody directed to alpha synuclein.

10. A pharmaceutical formulation comprising the blood brain barrier shuttle of claims 1 to 9 and a pharmaceutical carrier.

11. The blood brain barrier shuttle of claims 1 to 9 for use as medicament.

12. The blood brain barrier shuttle of claims 1 to 9 to transport the brain effector entity across the blood brain barrier.