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 ~~OF THE INVENTION~~

In a first aspect the present ~~invention~~ disclosure provides a blood brain barrier shuttle comprising a brain effector entity and a brain targeting peptide comprising a three amino acid peptide motif

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 ~~invention~~ provides a pharmaceutical formulation comprising the blood brain barrier shuttle of the present disclosure ~~invention~~ and a pharmaceutical carrier.

Furthermore, the present disclosure ~~invention~~ 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 use of the blood brain barrier shuttle of the present disclosure in the manufacture of a medicament.

In a fifth 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.

~~Aspects of t~~The disclosure ~~invention~~ 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 ~~aspect~~ embodiment of the disclosure~~invention~~, 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,

2-methoxyoestradiol, proliferin-related protein, carboxiamidotriazole, CMI 01, Manmastat, pentosan polysuiphate, angiopoietin 2 (Regeneron), interferon-alpha, herbimycin A, PNU 1451 56E, 16K prolactin fragment, Linomide, thalidomide, pentoxifylhne, genistein, TNP-470, endostatin, paclitaxel, Docetaxel, polyamines, a proteasome inhibitor, a kinase inhibitor, a signaling peptide, accutin, cidofovir, vincristine, bleomycin, AGM-1470, platelet factor 4 and minocycline. In yet another embodiment~~aspect~~, a cytokine may be selected from the group consisting of interleukin I (IL-I), IL-2, IL-5, IL-10, IL-11, IL-12, IL-18, interferon-γ (IF-γ), IF-a, IF-, tumor necrosis factor-ct (TNF-ct), or GM-CSF (granulocyte rnacrophage

colony stimulating factor). In still further embodiments of the disclosure~~invention~~, the agent may be a virus, a bacteriophage, a bacterium, a liposome, a microparticle, a magnetic bead, a yeast cell, a mammalian cell or a cell. In certain ~~aspects~~embodiments, the virus is a lentivirus, a papovaviruses, a simian virus 40, a bovine papilloma virus, a polyoma virus, adenovirus, vaccinia virus, adeno-associated virus (AAV), or herpes virus. The agent may also be a eukaryotic expression vector, and more preferably a gene therapy vector.

The brain targeting peptides of the disclosure ~~invention~~ may be attached to a solid support, e g, an array or bead. Embodiments of the disclosure ~~invention~~ may also include an isolated peptidomimetic comprising a sequence that mimics a peptide motif selected from the group consisting 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), or a peptidomimetic comprising a sequence that mimics a peptide consisting of Seq. Id. No. 1 to Seq. Id. No. 36, wherein the peptide is enriched in CSF and the brain.

Further embodiments include methods of targeting the delivery of an agent to CSF and brain, or vasculature thereof, in a subject, by obtaining an inventive brain targeting peptide as described herein or according to the inventive methods described herein, operatively coupling the peptide to the agent, and administering the peptide-coupled agent to the subject. A subject may be, but is not limited to, a primate, a monkey, a human, a mouse, a dog, a cat, a rat, a sheep, a horse, a cow, a goat or a pig. The agent can be a drug, a chemotherapeutic agent, a radioisotope, a pro-apoptosis agent, an anti-angiogenic agent, an enzyme, a hormone, a cytokine, a growth factor, a cytotoxic agent, a peptide, a protein, an antibiotic, an antibody, a Fab fragment of an antibody, an imaging agent, an antigen, a survival factor, an anti-apoptotic agent, a hormone antagonist, a virus, a bacteriophage, a bacterium, a hormone, a micro-particle, a magnetic bead, a micro-device, a yeast cell, a mammalian cell, a cell or an expression vector.

BRIEF DESCRIPTION OF THE DRAWINGS