BMC Proceedings

BioMed Central

Oral presentation

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Drug targeting to the brain

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from Infectious diseases of the nervous system: pathogenesis and worldwide impact
Paris, France. 10–13 September 2008

Published: 23 September 2008

BMC Proceedings 2008, **2**(Suppl 1):S37

This abstract is available from: http://www.biomedcentral.com/1753-6561/2/S1/S37

Many brain diseases (such as meningitis, encephalitis, multiple sclerosis (MS), stroke, brain tumors, epilepsy, Alzheimer's disease, AIDS related dementia, Parkinson's disease) are under treated or cannot be treated at all due to the presence of the barriers in the brain (blood-brain barrier, blood-cerebrospinal fluid barrier and the brain-cerebrospinal fluid barrier). The blood-brain barrier is facing the blood side and is the largest barrier for transport of macromolecular drugs from blood to brain. Therefore, targeting strategies to the BBB are necessary to selectively and specifically transport macromolecular drugs to the brain. This can be accomplished by exploiting receptor-mediated transport (RMT) systems at the blood-brain barrier. Moreover, enhanced selectivity can be obtained by targeting transport systems induced during disease conditions. Macromolecular protein drugs can be directly linked to a carrier molecule that fits to a RMT system. However, such applications often result in decreased activity of the resulting (fusion) protein and are prone to induce activation of and subsequent degradation by the immune system. Therefore, liposomal systems coated with carrier molecules are an alternative to deliver macromolecular protein drugs to the brain by targeting them to the blood-brain barrier.

A second, alternative approach may be to target genes to the brain. However, in our opinion it will be very difficult to transport such genes across the BBB. Our approach is to use the blood-brain barrier as a "protein factory" following delivery of genes encoding therapeutic proteins to the blood-brain barrier. Such proteins can be excreted by the blood-brain barrier endothelial cells to subsequently perform their therapeutic action in the brain. Genes can be attached to poly-cationic polymers like poly-ethyleneimines or incorporated into liposomal systems and targeted to the brain by a carrier molecule that fits to a RMT system.

For this purpose we use a human applicable carrier protein known as CRM197. CRM197 is the non-toxic mutant of diphtheria toxin that uses the membrane-bound precursor of heparin-binding epidermal growth factor (HB-EGF) as its transport receptor [1]. Membrane bound HB-EGF is constitutively expressed on the blood-brain barrier Moreover, HB-EGF expression is strongly up-regulated on cerebral blood vessels in diseases with inflammatory events like Alzheimer's disease, Parkinson's disease, MS, stroke/ischemia, tumors, epilepsy and encephalitis. This may provide disease induced drug targeting to the brain. Research so far has shown *in vitro* proof of principle for the transport of biopharmaceuticals across the BBB [2-4]. Therefore, this brain drug delivery technology holds out a great promise for future therapeutic applications.

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