Introduction

The blood-brain barrier (BBB) is a major obstacle to treatment of CNS disorders with biologics such as enzyme replacement therapy.

One strategy for creating brain-penetrant biologics is to target BBB receptors, such as the low-density lipoprotein receptor-related protein-1 (LRP1). This receptor has a number of inherent biochemical advantages for drug transport across the BBB. These include high capacity, rapid turnover, recognition of numerous ligands, and limited down-regulation.

In endothelial cells as at the BBB, LRP1 functions as to bring ligands into and across the cell via receptor-mediated transcytosis.

In non-endothelial cells, LRP1 functions as a scavenging receptor, directing ligand transport into the lysosome via receptor-mediated endocytosis.

We have created peptides (Angiopeps), including Angiopep-2 (An2) using a library based on LRP1 binding sequences of known LRP1 ligands. These peptides can be introduced, by chemical conjugation or recombinant fusion, to small molecules and biologics, thus forming NCEs that are brain-penetrant Peptide-Drug Conjugates.

Clinical Proof of Concept: ANG1005 (An2-paclitaxel)

Conjugation of paclitaxel, which does not cross the BBB, and An2 has created a brain-penetrant chemotherapeutic New Chemical Entity that crosses the BBB.

Phase 1 and Phase 2a trials completed in patients with brain tumors:
- Tolerability profile similar to paclitaxel
- Efficacy in high dose group including MTD: Phase 1:
  - Brain Mets (n=21): 71% with tumor shrinkage or stabilization
  - Recurrent Gloma (n=28): 61% tumor shrinkage or stabilization, including 2 complete responders
- Efficacy at 550 mg/m², Phase 2a:
  - BC Brain Mets (n=8): 61% tumor shrinkage or stabilization

ANG1005 development continues with two Phase 2 clinical trials:
- Phase 2a in recurrent glioma - started October 2013
- Phase 2b in breast cancer with brain metastases – starting Q1 2014

Preclinical Proof of Concept: Green Fluorescent Protein (GFP)

Uptake of An2-GFP in brain endothelial cells (in vitro)

Brain-penetrant An2-GFP (in vivo)

Conclusions

While other receptor-mediated transcytosis systems have shown preclinical data, the LRP-1 strategy is the only one with clinical validation.

Clinical validation:
- CNS responses seen in breast cancer brain metastases (Ph2), glioma (Ph1/2), brain metastases from various cancers (Ph1/2)

Pre-clinical validation:
- Enzymes, monoclonal antibodies, peptides
- All show increased transport into the CNS when linked to Angiopeps.