INTRODUCTION
HER2+ Brain Metastases

Chemotherapy for malignant brain tumors often has limited efficacy, largely due to restricted blood–brain barrier (BBB) permeability for chemotherapeutic drugs. Angiochem’s proprietary Angiopep peptides target the low-density lipoprotein receptor-related protein (LRP) receptor. This endogenous transcytosis system has a number of inherent biochemical advantages for drug transport across the BBB, including high expression, rapid turnover, numerous ligands of varying sizes, and limited down-regulation.

ANG1005 is the first compound developed using our peptide-drug conjugate platform for the treatment of primary and secondary brain cancers. Phase 1/2 clinical trials in humans have been completed. ANG1005 reached therapeutic concentrations in brain tumors and produced significant antitumor responses in patients with primary gliomas or secondary brain metastases. These peptides can be introduced to small molecules and biologics, thus forming NCEs that are brain-penetrant Peptide-Drug Conjugates.

ANG4043 retain anti-HER2 principal characteristics

- Affinity for the HER2 receptor of the mAb is unaffected by incorporation of An2.
- The anti-proliferative potency of ANG4043 is similar to that of anti-HER2 mAb.
- ANG4043 plasma PK is also similar to native mAb.

Warning: ANG4043 is not a biosimilar.

ANG4043 is a chemical conjugate of the anti-HER2 mAb with the peptide Angiopep-2 (An2).

ANG4043 is a humanized Anti-HER2 mAb.

ANG4043 Reduces Tumor Size

Brain uptake of An2-HER2 derivatives (in situ brain perfusion)

Effect of anti-HER2, ANG4043 and An2-anti-HER2-drug conjugates on BT-474 cell proliferation. Cancer cells were incubated for 5 days with the drugs. [3H]-Thymidine incorporation assay was then performed for IC50 evaluation.

Brain uptake of ANG4043 was measured by in-situ brain perfusion in mouse brain demonstrates that Angiopep-2 Anticancer Drugs Conjugates better penetrate the brain than unconjugated drugs.

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Conclusions

- The brain-penetrant An2-anti-HER2 mAb conjugate, ANG4043, targets intracranial tumors and shrinks tumor size in mice, indicating that therapeutic concentrations have been achieved in brain.
- This reduction in tumor size translates to a significant increase in survival in mice with intracranial HER2+ (BT-474 cell) tumors.
- Two anticancer drugs (docetaxel and maytansine) have been conjugated to An2-anti-HER2 derivatives.
- Both drugs showed increased anti-proliferative activities and BBB permeability when compared to unconjugated anti-HER2 mAb.
- These new brain penetrant An2-anti-HER2-drug conjugates (An2-ADCs) could further improve mouse survival observed with ANG4043.

Utilization of the Angiopep platform to enable brain penetration of therapeutic mAbs or Antibody-Drug Conjugates for treatment of brain tumors

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Angiopep Technology

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