ABSTRACT

The blood-brain barrier (BBB) is mainly formed by brain capillary endothelial cells which are closely-sealed by tight junctions and express high levels of active efflux transport proteins, including P-glycoprotein (P-gp). As a result, the overwhelming majority of small molecules, proteins and peptides do not cross the BBB. Angiochem’s engineered peptide compound (EPC) provides a non-invasive and feasible platform for small and large molecules to break the BBB. Contained in this presentation, we will discuss a series of new drug entities composed of small molecules, peptides and MAbs. The most advanced of which is ANG1005 (ANG), a novel agent that can create a portfolio of new drug entities composed of EPCs, peptides and MAbs. The key advance of which is ANG1005, and we have created a portfolio of new drug entities composed of small molecules, peptides and MAbs. The key advance of which is ANG1005, and we have created a portfolio of new drug entities composed of small molecules, peptides and MAbs. The key advance of which is ANG1005, and we have created a portfolio of new drug entities composed of small molecules, peptides and MAbs. The key advance of which is ANG1005.

RESULTS

ANGIOPEP-2

In vitro anticancer activity

A. Etoposide-Angiopep-2

B. Doxorubicin-Angiopep-2

Two new anticancer drugs were generated by conjugating three molecules of etoposide (A) or doxorubicin (B) on one molecule of Angiopep-2. The new drug entities were tested in vitro for their ability to inhibit cell proliferation of several cancer cell lines. The results showed that the new drugs demonstrated higher anti-cancer activities compared to unconjugated etoposide or doxorubicin. In addition, the new drugs showed better penetration into the brain tissue compared to unconjugated molecules.

INHIBITION OF CANCER PROLIFERATION IN VITRO

Effect of Etoposide-Angiopep-2 and Doxorubicin-Angiopep-2 on cancer cell proliferation. Cancer cells were incubated for 48 h with the new anticancer conjugates or with the unconjugated drugs. [3H]Thymidine incorporation assay was then performed to evaluate their IC50 values.

CONCLUSIONS

• In addition to ANG1005 which shows promising results in Phase 1/2 studies (Abstracts #3781 and #3782), two new anticancer etoposide and doxorubicin derivatives have been generated using the Angiopep-2 platform.
• Both new anticancer drugs: - Inhibit cancer cell proliferation in vitro with low IC50 values - Have a better brain penetration than unconjugated drugs - Bypass the efflux pump (P-gp, MDR1) - Show a better brain and tumor distribution than unconjugated drugs
• Work is on-going to evaluate their in vivo efficacy.