ET-09 : A new drug, ANG1005, a conjugate of Paclitaxel and Angiopep peptide vector able to cross the Blood-Brain Barrier for the treatment of brain cancers.

Reinhard Gabathuler1, Michel Demule2, Anthony Régina3, Christian Ché4, Paul Lockman5, Fancy Thomas6, Julie Gasch7, Helen Thorisheim8, Abedelhasser Abulrob9, Quentin R. Smith9, Danica Stanimirovic1, Richard Béliveau1 and Jean-Paul Castaigne1.
1Angiochem Inc., Montréal, QC, Canada. 2Université du Québec à Montréal, Montréal, QC, Canada. 3Texas Tech University HSC, Amarillo, TX. and 4NR Institute for Biological Sciences, Ottawa, ON, Canada.

ABSTRACT

The brain tumor barrier (BBB) is mainly formed by brain capillary endothelial cells which are closely sealed by tight junctions. This barrier efficiently prevents a vast array of drugs to cross into brain parenchyma. The BBB is essential for maintaining cellular homeostasis, but it also impedes the delivery of therapeutic molecules to brain tumors. Although advanced drug delivery technologies (Angiopeps) reduce this barrier and facilitate drug translocation into the brain, these approaches are not specific to brain tumors. ANG1005, a targeted conjugate of Angiopep and Paclitaxel, is a novel drug delivery system that can bypass the BBB and deliver therapeutic drugs to tumor cells located within the brain. The purpose of this study was to evaluate the effect of ANG1005 on brain tumor distribution and to determine if it can overcome the BBB after intravenous injection in mice. ANG1005 was intravenously administered at a rate of 5 mL/min for 10 minutes. ANG1005 conjugates showed high distribution in brain tumors compared to the negative control Angiopep-2, demonstrating that ANG1005 is capable of overcoming the BBB and delivering therapeutic agents to brain tumors.

EXPERIMENTAL MODELS

1. Brain tumor distribution after IV injection of fluorescent conjugates (Angiopep-2 FITC and Angiopep-2 Cy5.5) in nude mice intracranially implanted with U87MG cells. ANG1005 was intravenously administered at a rate of 5 mL/min for 10 minutes.

2. Brain capillary distribution of fluorescent conjugates (Angiopep-2 Cy5.5 and Angiopep-2 FITC) in nude mice intracranially implanted with U87MG cells. ANG1005 was intravenously administered at a rate of 5 mL/min for 10 minutes.

3. Normal brain uptake of ANG1005 after IV injection in mice. ANG1005 was intravenously administered at a rate of 5 mL/min for 10 minutes.

CONCLUSIONS :

- ANG1005 is rapidly transported to brain parenchyma.
- ANG1005 shows higher distribution in brain tumors.
- ANG1005 transports into brain parenchyma is 100 times higher than paclitaxel.
- ANG1005 distributes homogeneously in brain regions.
- ANG1005 delivers therapeutic concentrations of paclitaxel to the brain.
- ANG1005 inhibits intracranial tumor growth as measured by MRI in rats.

REFERENCES:

Demeule et al., J. Neurochem. 105(1), 133-144, 2008
Regine et al., J. Pharm. Pharmacol. 58(15), 165-177, 2006