Material and Methods: An *in vitro* model of the BBB and *in situ* brain perfusion were used to assess the brain uptake of Taxol-conjugate. Xenograft models of glioblastoma (U87) and non-small cell lung carcinoma (NCI-H460) were established by subcutaneous (s.c.) injections of cancer cells in immunodeficient mice nu/nu. Moreover, glioblastoma as well as lung brain metastasis models were also established by intracranial stereotaxic injections of U87 and NCI-H460 cells, respectively.
Results: We demonstrate here the transcytosis ability of peptides derived from kunitz domain called Angiopeps using an *in vitro* model of the BBB and *in situ* brain perfusion. Angiopep transcytosis across bovine brain capillary endothelial cell (BBCEC) monolayers is at least 19-fold higher than that of holo-transferrin. In addition, Taxol, has been conjugated to these vector-peptides (Angiopeps). Importantly, Taxol-Angiopep conjugate has a similar effect than free Taxol on cancer cell proliferation *in vitro*. However, the conjugation of Taxol to Angiopep allows to bypass P-gp leading to a higher accumulation of Taxol in the brain parenchyma. We also found that Taxol-Angiopep conjugate caused a stronger inhibition of the s.c. tumor growth of U87 and NCI-H460 than free Taxol. Moreover, Taxol-Angiopep conjugate significantly increased survival of mice implanted with intracranial NCI-H460 and U87 cells by 27 and 24%, respectively.
Conclusion: Overall, these results indicate that the conjugation of Taxol with Angiopep-vector increases the effect of Taxol on tumor growth as well as Taxol accumulation in brain. Furthermore, in primary and secondary brain tumor models, Taxol-Angiopep conjugate administration prolonged mice survival.

148 POSTER

Self-assembling nanoparticles targeting G-protein coupled receptors and ABC transporters

N. Tarasova. *NCI-Frederick, Structural Biophysics Laboratory, Frederick, MD, USA*

We have previously shown that synthetic analogs of the transmembrane domains (TMs) of G-protein coupled receptors (J Biol Chem 1999; 274(49): 34911–5) and of the multiple drug resistance protein, P-gp (J Med Chem 2005; 48(11): 3768−75) efficiently and specifically inhibit the function of the target protein. The remarkable feature of these inhibitors is that they can be designed rationally solely on the basis of the primary structure of the protein.
A transmembrane antagonist of CXCR4 incorporated in lipid liposomes was shown to completely inhibit metastasis in a mouse model of breast cancer. We have found recently that liposomes may not be needed for the delivery of TM antagonists.

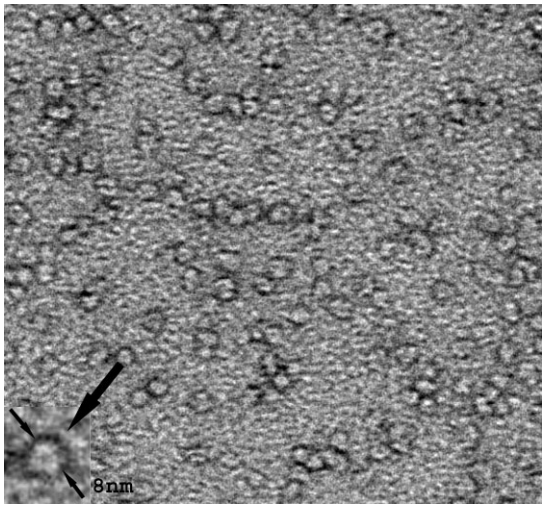

Fig. 1. Cryo-elecron microscopy of the transmembrane antagonist of CXCR4 receptor CXCR4−2–2 demonstrated self-assembly of the compound into nanoparticles with a diameter about 8 nm.

Experiments utilizing multiple angle light scattering have shown that TM peptides self-assemble into stable nanoparticles in aqueous solutions. Cryo-elecron microscopy has revealed formation of uniform particles with a diameter of about 8 nm, which is within the presumed optimal range for intra-tumor delivery. Electron microscopy studies of numerous “mutant” peptides have shown that negative charges added to the C-terminal end of the peptides were critical for formation of small uniform particles. Many TM peptide micelles aggregated further forming rings and strings. Addition of short polyethylene glycol chains reduced aggregation, while PEG chain consisting of 39 repeats provided for non-aggregating and uniform nanoparticles. NMR, light scattering and calorimetry studies have demonstrated remarkable stability of TM peptide micelles with CCM in low micromolar range.
Nanoparticular forms of transmembrane peptides retained full biological activity. CXCR4-targeting TM micelles inhibited signaling through the receptor, while ABCG2 and P-glycoprotein TM nanoparticles inhibited drug efflux mediated by the corresponding transporter. Nanoparticles formed by TM peptides also efficiently encapsulated poorly soluble hydrophobic drugs, thus providing a unique delivery system with dual anti-tumor activity. Self-association of transmembrane peptides in aqueous solutions is a novel phenomenon. It enables the development of new methods of specific and rational targeting of integral membrane proteins *in vivo* and provides for a new paradigm in drug development where the drug itself self-assembles in a nanostructure that has the desired size and surface properties for intra-tumor delivery.

149 POSTER

Pharmacokinetics of irinotecan and its metabolites after i.v. administration of IHL-305, a novel PEGylated liposome containing irinotecan, to tumor-bearing mice

A. Kurita, T. Furuta, N. Kaneda, I. Kato, S. Sawada, M. Onoue. *Yakult Honsha Co., Ltd., Yakult Central Institute for Microbiological Research, Tokyo, Japan*

Background: IHL-305 is a preparation of irinotecan encapsulated in PEGylated liposome. IHL-305 demonstrated stronger tumor growth inhibition effect than irinotecan hydrochloride (CPT-11) on various human cancer xenografts such as the colon, lung, gastric, ovarian, and prostate cancer cell lines. Liposome preparations are selectively transported to tumor tissues by the enhanced permeability and retention (EPR) effect. In this study, we compared the pharmacokinetics after i.v. administration of IHL-305 with CPT-11 in tumor-bearing mice.
Materials and Methods: Female BALB/c mice transplanted with Meth A tumors were i.v. administered with IHL-305 or CPT-11 at a dose of 16.7 mg/kg, and were exsanguinated at 8 time points until 96 hours after dosing, followed by extirpation of the tumor, liver and kidney. The concentrations of irinotecan and its metabolites, SN-38, and SN-38 glucuronide (SN-38G), in plasma and these tissues were measured.
Results: The plasma irinotecan, SN-38, and SN-38G concentrations peaked at 0.167, 6, and 12 hours after IHL-305 dosing, respectively, whereas those after CPT-11 dosing peaked at 0.167 hours. The AUC_{0-inf}, C_{max}, and $t_{1/2}$ of irinotecan after IHL-305 dosing were higher than those after CPT-11 dosing (302-, 55-, and 2.9-fold, respectively). The C_{max} of SN-38 and SN-38G after IHL-305 dosing were lower than those after CPT-11 dosing (0.13- and 0.23-fold), however, the AUC_{0-inf} were higher (2.5- and 1.8-fold), because of their much slower disappearance than CPT-11 dosing. Irinotecan and SN-38 concentrations in tumor tissue after CPT-11 dosing peaked at 0.167 and 0.5 hours, followed by a relatively rapid decrease. Concentrations after IHL-305 dosing remained nearly constant up to 12 hours for irinotecan and 48 hours for SN-38 and then decreased gradually. Their AUC_{0-inf} were higher than those after CPT-11 dosing (9.02- and 3.89-fold). The AUC_{0-inf} of irinotecan and SN-38 in the liver and kidney tissues after IHL-305 dosing were also higher than those after CPT-11 dosing (15- and 2.3-fold for the liver, and 4.1- and 2.4-fold for the kidney, respectively).
Conclusion: The irinotecan and SN-38 concentrations in plasma, tumor, liver, and kidney tissues after IHL-305 administration to tumor-bearing mice were markedly higher than those after CPT-11 dosing. The AUC ratio of SN-38 between CPT-11 and IHL-305 administration in tumor tissue was greater than in the liver and kidney, suggesting that targeting was improved by its liposomal formulation.

150 POSTER

Effects of dasatinib on the pharmacokinetics of simvastatin, a cytochrome P450 3A4 substrate, in healthy subjects

C.-Y. Wu, F. Callegari, K. Williams, A. Sanil, T. Griffin, A. Blackwood-Chirchir. *Bristol-Myers squibb, Pharmaceutical Research Institute, Princeton, USA*

Background: Dasatinib – an oral inhibitor of multiple oncogenic kinases – has demonstrated clinical efficacy in CML and Ph+ ALL. *In vitro* dasatinib inhibits CYP3A4 (IC_{50} =1.9 μM). The objective of this study was to assess the effect of dasatinib on simvastatin plasma concentration–time profiles in healthy subjects.
Methods: Healthy subjects (N = 48) were treated in this open-label, randomized, two-period, two-treatment, balanced, crossover study. The treatments were: A) 80 mg simvastatin (single dose) (control); and B) 80 mg simvastatin plus 100 mg dasatinib (both single doses). Blood samples for