ANG-1005 in Patients with Brain Metastases from Breast Cancer: Correlative Imaging with 18F-FLT-PET/CT

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Background: ANG1005 (formerly GRN1005) is a novel drug conjugate consisting of 3 paclitaxel molecules covalently linked to Angiopep-2 designed to cross the blood brain barrier via endocytosis after binding the low-density lipoprotein (LDL) receptor-related protein (LRP). In development for taxane-sensitive brain metastases, a multi-center, single-arm study with the primary endpoint of intra-cranial overall response rate in patients with brain metastases from breast cancer is ongoing. Since MRI detection of brain metastases utilizes gadolinium leakage rather than actual tumor volume, new assessment methods are needed. A pilot study at the NCI enrolled patients to evaluate the utility of 18F-FLT (3’-fluoro-3’ deoxythymidine)-PET.

Methods: Patients with measurable brain metastases from breast cancer were eligible. ANG1005 was administered IV at 550 mg/m2 q 21 days. MRI imaging with gadolinium was used to determine clinical response, and compared to 18F-FLT PET/CT imaging performed before and after cycle 1. FLT incorporation reflects DNA synthesis. Dynamic scans were obtained over 30 min and a static whole body PET image at 1 hour. The % change in standard uptake value (SUV) before and after ANG1005 was determined, considering a significant change > 20%.

Results: Eighteen metastatic brain lesions in eight patients were analyzed with FLT PET. The maximum (SUVmax) ranged from 0.8 to 4.0 at baseline, mean 1.8. Tumor to normal (T:N) ratios ranged from 2.9 to 22.3, mean 7.7. Twelve of the 18 lesions showed a >20% decrease post-therapy. The average % change in SUVmax was -24.8% (11 to -66.8%), and T:N ratios -7.7%. The FLT-PET response was frequently discordant with the MRI result. Two patients had confirmed partial responses with durations of response of 6 and 13 cycles. One patient had an unconfirmed PR, with progression after 6 cycles. Two patients had stable disease, receiving 6 and 8 cycles.

Conclusion: Therapy for CNS metastases from breast cancer is an important unmet need, as is assessment of therapeutic outcome. ANG1005 is a paclitaxel conjugate with demonstrated activity designed to cross the blood-brain barrier. Pilot evaluations of FLT-PET imaging of brain metastases suggest it is a promising tool for detection and measurement of CNS disease.
Using modified Clostridium sporogenes as a delivery vehicle for anti-cancer therapeutics

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Background: Clostridium sporogenes is part of a highly diverse group of Gram positive, spore forming, anaerobic bacteria. C. sporogenes can be used as a delivery vehicle for chemotherapeutics in cancer treatment due to the inactive spore form of C. sporogenes only germinating in the microenvironment of the hypoxic tumour. The directed enzyme pro-drug therapy (DEPT) strategy has been tested with several different delivery vectors, and Clostridial DEPT (CDEPT) has previously been developed with one pro-drug converting enzyme (nitroreductase). In this treatment the non-toxic pro-drugs are administered to the patient, then a pro-drug converting enzyme is delivered through genetically altered C. sporogenes. This enzyme breaks the pro-drug down into a toxic component. The aim of this project is to develop the system further with an alternative pro-drug converting enzyme which digests its potential substrate into a 100 fold more toxic subcomponent.

Materials and Methods: To efficiently implement the use of this enzyme in the CDEPT strategy, the delivery system needed to be optimised to allow for its effective export and binding to the cell wall of the bacteria to maintain site specificity. To do this, the use of a panel of different signal peptides was investigated. Concurrently to that different sortase signal motifs were identified in Clostridium species through psiBLAST, and their use to anchor the protein to the cell wall was investigated. Successful attachment and protein export was judged by assaying the presence of enzyme activity in the different fractions of bacterial cultures.

Conclusion: Results showed an enhanced export of the enzyme into the culture supernatant, and significant cell wall anchoring. This data gives a good basis from which development of an optimized CDEPT system should be achievable, which would result in a highly site specific, hypoxic tumour therapy system.
P2.06

Curious controlled release of flutamide-related escape products under exposure to magnetic fields

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Introduction: Flutamide (FM: 2-methyl-N-[4-nitro-3-(trifluoromethyl)phenyl]propanamide) is a non-steroidal anti-cancer drug, and is widely applied to recent drug delivery technologies. Several reports also have shown the photoreactivity of FM in phospholipid bilayer vesicles (liposomal membranes). However, there are no reported studies of the application of radical pair mechanisms to drug release controlling of FM-incorporated liposomal carriers under exposure to magnetic fields. In this study, we investigated magnetic controls of the carriers for an advantageous release of flutamide-related escape products.

Materials & methods: Egg yolk phosphatidylcholine (PC) or Dipalmitoylphosphatidylcholine (DPPC) was used as the lipid component of liposomes. FM-incorporated multilamellar vesicles (FM-MLVs) were prepared according to the previous method [1]. FM-incorporated small unilamellar vesicles (FM-SUVs) were prepared by the membrane filtration method [2]. All operations were carried out under nitrogen. FM-related escape products were monitored measuring the delayed fluorescence (ex. 530 nm, em. 890 nm) of the products. The magnetic field strength was set up in the range of 50–150 mT.

Results: For measurements of magnetic field effects on release of FM-related escape products, the decrease in the products is due to S-T level intersystem crossing on radical pair mechanisms. When PC was used as the lipid component of the FM-SUVs, competition between magnetic field effects and the product release was observed depending on the field strength. In the case of the FM-SUVs prepared from DPPC lipid molecules, the increase in the product release was relatively faithful to S-T Intersystem.

Conclusions: From these findings, the product release is deemed not to be caused by only the radical pair mechanisms. However, the tests observing the magnetic field effects might provide useful in formation on drug targeting.


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