

Tiny Trojan horses attack brain cancer cells

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Scientists in Germany have developed a way of smuggling an anti-cancer drug past the protective blood-brain barrier and into brain tumours and metastases using a nanocarrier – a tiny capsule specially designed to pass through cell membranes and deliver its anti-cancer drug to the cancer cell.

The blood-brain barrier is formed by a network of closely sealed endothelial cells in the brain's capillaries, and it expresses a high level of proteins that pump foreign molecules away from the brain, while allowing others (such as glucose and insulin) that are necessary to the functioning of the brain cells to cross the barrier. This makes it very difficult for molecules, including anti-cancer drugs, to cross the bloodbrain barrier and reach tumour cells in the brain. Currently, less than five per cent of drugs are able to cross the barrier and new therapies are needed urgently.

In the research presented today at the 22nd EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics in Berlin, the scientists describe how they designed the nanocarrier with lipid membranes encapsulating and protecting an anti-cancer drug, mitoxantrone, and harnessed it to an existing technology, Angiopep, to get through the blood-brain barrier. Angiopep is a small peptide (amino acid compound) that has been designed to reach brain cells by making use of the receptors on the surface of the blood-brain barrier that are responsible for actively transporting necessary molecules through the barrier to the brain.



The nanocarrier, or Trojan Horse Liposome (THL), has a diameter of between 100-120 nanometres (a nanometre (nm) is one billionth of a metre), equivalent to 1000th the size of a fine grain of sand or 400 time smaller than a human hair. In laboratory membrane experiments, the researchers found that the THL was effective at being taken up by epithelial and glioma cancer cells. Then they tested it on mice with brain metastases from breast tumours and found that the THL was more effective at reducing tumour growth than when mitoxantrone was given on its own (free mitoxantrone). In addition, the THL-treated mice had far fewer side effects, such as gastrointestinal complications, weight loss and dehydration.

Mrs Andrea Orthmann, a PhD student who is working on the project under the supervision of Dr Reiner Zeisig and Dr Iduna Fichter in the Experimental Pharmacology group at the Max-Delbrück Centre for Molecular Medicine, Berlin (Germany), said: "The data show that the THLs are significantly better at reducing tumour growth than the free drug mitoxantrone, or mitoxantrone encapsulated in liposomes without the Angiopep ligand. The THLs reduced the tumour area by 73% in comparison to the untreated control group, and by 45% in comparison to free mitoxantrone. The second important point is the characterisation of side effects. We measured the body weight, blood parameters and the general conditions of the animals. We observed intolerances as a result of the treatment with the free drug (much body weight loss, gastrointestinal disorders, dehydration, pathologic skin and haematology toxicity). All of these side effects were prevented if THLs were used."

The reason why there were fewer side effects with the THL treatment was because the lipid membranes of the THLs protected the anti-cancer drug from affecting or being affected by the rest of the body. "This results in a clear reduction of <u>side effects</u>, which are usually the most serious concerns of anti-cancer drugs," said Mrs Orthmann.



She said that one of the exciting aspects of the research was its potential for use with other drugs and in other cancers and diseases. "Our Trojan Horse Liposomes represent a platform technology that enables the nanocarrier to be loaded easily with different drugs without any chemical modification. In addition, the Angiopep ligand could be replaced by other targeting molecules without too much additional effort. This means that the liposomes have the potential to be used in several other diseases, including neurodegenerative ones such as Alzheimer's, Parkinson's and Huntingdon's disease, as well as other tumours or metastases."

However, there is much work to be carried out first before this technology can enter the clinic. The researchers need to perform more laboratory research to improve the treatment of <u>brain tumours</u> and metastases and to investigate further the mechanism of drug delivery. "Our results demonstrate that the obstacle in the chemotherapeutic treatments of brain tumours and metastases in the brain can be overcome by our Trojan Horse Liposomes which are capable of improved transport through the blood-brain barrier," concluded Mrs Orthmann.

Provided by ECCO-the European CanCer Organisation

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