NEWS RELEASE

20th EORTC-NCI-AACR SYMPOSIUM on "Molecular Targets and Cancer Therapeutics" Geneva, Switzerland, 20-24 October 2008

Embargoed: 12.15 hrs CEST, Wednesday 22 October 2008
NB: this will be the subject of a news briefing by Dr Reinhard Gabathuler and Dr Jean-Paul Castaigne at 12.15 CEST on Wednesday 22 October in the press conference room (Room F in Hall 2)

Crossing the blood-brain barrier: scientists develop a new drug delivery system for brain cancers and other, hard-to-treat diseases of the central nervous system

Geneva, Switzerland: Scientists have developed a new drug delivery system that is capable of crossing the blood-brain to reach and kill cancer cells in the brain, according to research presented at the 20th EORTC-NCI-AACR [1] Symposium on Molecular Targets and Cancer Therapeutics in Geneva today (Wednesday 22 October). Following successful preclinical studies, the technology is being evaluated in two phase I clinical trials in patients with malignant glioma and brain metastases.

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 blood-brain barrier and reach tumour cells in the brain. Currently, less than five per cent of drugs (made up of very small molecules) are able to cross the barrier; one example is temozolomide, which is the only chemotherapy available for treating brain tumours such as glioblastoma multiforme and progressive anaplastic astrocytoma. These tumours have a poor prognosis and continue to grow, even after treatment with temozolomide. Therefore, new therapies for these hard-to-treat brain tumours are needed urgently.

In four, related presentations to the symposium, scientists from Canada, the USA and France described how they are investigating a new drug delivery technology that provides a non-invasive and flexible way of transporting different drugs (for example, antibodies, proteins, peptides, siRNA, small molecules, etc.) across the blood-brain barrier and into the central nervous system.

The drug being evaluated in the four abstracts is called ANG1005. It is made up of one molecule of a peptide called Angiopep-2 joined together with three molecules of paclitaxel, a taxane chemotherapy drug.

Dr Reinhard Gabathuler, author of one of the abstracts and chief scientific officer at Angiochem Inc (Montreal, Canada) – the company that is developing the Angiopep technology and ANG1005 – explained: "Unlike invasive or pharmacological approaches to deliver drugs to the brain, the Angiopep technology utilises the physiological approach by making use of the receptors on the surface of the blood-brain barrier that are responsible for actively transporting necessary molecules across the barrier to the brain. The family of Angiopeps (including Angiopep-2) has been designed to interact with a specific receptor, Low Density Lipoprotein Receptor Related Protein-1 (LRP-1). This receptor has many functions, binds over 30 ligands [molecules] of various sizes, and is highly expressed at the blood-brain barrier."

In laboratory-based tests of ANG1005 on mice and rats, Dr Gabathuler, internal scientists and collaborators in the US and Canada found that the drug was transported rapidly across the blood-brain barrier and into the functional part of the brain, the parenchyma.

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"In contrast to free paclitaxel, which is normally prevented from reaching the brain by the P-glycoprotein efflux pump, ANG1005 is efficiently transported across the blood-brain barrier, with approximately 100-fold higher transport rate compared to free paclitaxel and 10-fold higher transport rate than temozolomide," he said.

In addition, the drug resulted in a significant, 27% increase of survival of mice with glioblastoma tumours and a shrinking of glioblastoma tumours in rats.

A second study, led by Dr Francis Bichat, head of the scientific platform at Oncodesign (Dijon, France), evaluated the anti-cancer properties of the drug in cancer cell lines and mice, as well as investigating its toxicity and what happened to the drug in mice.

He found that ANG1005 had the same anti-cancer properties as did free paclitaxel (paclitaxel on its own) in cancer cell lines. Speaking before the conference, he said: "The anti-tumour activity of paclitaxel was maintained with ANG1005 compared with free paclitaxel. There was no loss of activity." He also found a significant inhibition of brain tumour growth in rats when they were treated with ANG1005, whereas tumours in rats that were treated with paclitaxel did not have their growth inhibited. "This is probably because free paclitaxel is not able to enter the brain," he said.

"The most interesting finding from this study is the potency of ANG1005 to bypass the blood-brain barrier and to allow paclitaxel into the brain where it shows anti-tumour activity," said Dr Bichat.

The success of these pre-clinical studies enabled Angiochem Inc to start two phase I clinical trials at cancer centres in the US: one in patients with advanced cancer and brain metastases, and the second in patients with recurrent malignant glioma.

These trials are still being conducted, but, as of 23 September 2008, 22 patients with advanced solid tumours (including breast cancer, melanoma, liver cancer and 15 patients with brain metastases) have been treated with ANG1005 in the first trial. The drug is given by intravenous infusion for one hour, every 21 days. At doses up to 500 mg/m^2 the drug appears to be safe and well tolerated and no patient has discontinued due to adverse side-effects. The researchers are continuing to increase the dose.

Dr Jean-Paul Castaigne, president and chief executive officer of Angiochem Inc, who presented the clinical trials results, said: "To date, the safety and tolerability of ANG1005 has been excellent in patients with advanced solid tumours and brain metastases."

In the second trial in patients with recurrent malignant glioma, 12 patients had been treated by 23 September 2008 – eight with glioblastoma multiforme, one with anaplastic astrocytoma and three with anaplastic oligondendrocytoma.

Dr Castaigne said: "We have demonstrated that the drug is safe and tolerable up to and including doses of 75 mg/m^2 and we are currently evaluating doses of 105 mg/m^2. No patient has discontinued due to drug-related adverse side-effects. So far, all patients (with the exception of one) dosed up to 50 mg/m^2 have had their disease progress following two cycles of treatment at six weeks. However, it should be noted that 50 mg/m^2 of ANG1005 has an equivalent paclitaxel dose of only about 25 mg/m^2, which is still quite low for appreciable cytotoxic effects."

He continued: "To date, treatment options for patients with recurrent malignant glioma are limited and prognosis is bleak because of the brain's highly evolved physiological structure. Results from both these trials show that Angiopep conjugates may provide a potentially safe and effective way to treat gliomas and other currently unmanageable diseases of the central nervous system. The Angiopep technology is well tolerated, since most of the side-effects observed to date with ANG1005 are caused by paclitaxel, the active drug component."

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Both trials will be reporting their most important results by the end of 2008, and researchers are planning a continuation of the trial in patients with brain cancer in 2009.

Dr Castaigne said: "Angiochem's intention is to continue the early development of ANG1005 until proof-of-efficacy is obtained in either progressive malignant gliomas or brain metastases. We will seek to find a partner with significant oncology experience to carry forward the later development stages and marketing of ANG1005.

"Although other technologies have demonstrated abilities to cross the blood-brain barrier, we believe that the Angiopep technology is the furthest developed of the physiological approach and has significant advantages. ANG1005 is the company's first compound in clinical development using the Angiopep technology. We have been successful in conjugating other chemotherapeutics (e.g. doxorubicin and etoposide) to our technology; preclinical data have demonstrated success in delivering these compounds into the brain and retaining cytotoxic activities. Angiochem is also focusing considerable effort on the conjugation and delivery of other drug classes (including monoclonal antibodies, proteins, peptides, siRNA, etc.) to treat other CNS disorders."

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Abstract nos: 117 (Dr Reinhard Gabathuler), 139 (Dr Francis Bichat), 424 & 425 (Dr Jean-Paul Castaigne). Poster sessions in the poster area, 12.00 – 15.00 hrs CEST, Wednesday 22 and Thursday 23 October.

Notes:
[1] EORTC [European Organisation for Research and Treatment of Cancer, NCI [National Cancer Institute], AACR [American Association for Cancer Research].

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From 09.00 hrs CEST Tuesday 21 October to 14.30 hrs CEST Friday 24 October
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