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 Zheng Jim Wang at 12.15 CEST on Wednesday 22 October in press conference room in Hall 2

Researchers discover the anti-cancer drug bevacizumab can be used to detect and diagnose tumours in animal models using PET/CT imaging: results are better than current 'gold standard' method

Geneva, Switzerland: Scientists have developed a new imaging agent that can be used in scanning for tumours, and which gives a much clearer and more precise image than existing methods. The discovery has the potential to revolutionise pre-clinical cancer research and clinical diagnostic practice, and it makes use of compounds that have already been approved for treating patients: the anti-cancer drug bevacizumab (Avastin) and Copper-64, a radioactive copper nuclide, which is approved by the US Food and Drug Administration (FDA) for some clinical trials.

Dr Zheng Jim Wang told the 20th EORTC-NCI-AACR [1] Symposium on Molecular Targets and Cancer Therapeutics in Geneva today (Wednesday 22 October) that he and his colleagues had attached bevacizumab to a molecule called DOTA (a cyclic compound) and tagged it with a radioactive tracer, Copper-64 (64Cu). Bevacizumab is an antibody that targets vascular endothelial growth factor (VEGF), a signalling protein released by tumour cells and which plays an important role in angiogenesis (the process by which a growing tumour creates its own blood supply). Currently, bevacizumab is being used to treat patients with advanced colorectal cancer and is being tested in several other metastatic cancers.

When the researchers injected the compound (64Cu-bevacizumab) into mice with breast, lung and pancreatic cancers and then used PET/CT imaging to scan the animals, they found that it successfully targeted the cancer cells, accumulating in high concentrations in the tumours, and that it enabled clear and well-defined images of the tumours to be detected during scanning.

When compared with images of the same tumours in the same animals taken the day before, using the current gold standard imaging probe for tumours (18-Fluoro-Deoxy-Glucose (18FDG)), they found that not only were the 64Cu-bevacizumab images better, but also that they could detect tumours in earlier stages and at smaller sizes than with 18FDG. In addition, the 64Cu-bevacizumab images had none of the conventional "hot spots" that tend to appear in 18FDG images and which affect the accuracy of the imaging; "hot spots" occur where the compound has accumulated not just in tumours but also in key organs (such as the heart, brain, kidneys and bladder) which give false positive signals.

Dr Wang, Director of Molecular Imaging at MPI Research Inc (Michigan, USA) and an adjunct assistant professor at University of Texas Health Science Center at San Antonio, said: "Our collaborative research reveals and verifies a new imaging agent for the next generation of tumour detection imaging probes. 64Cu-bevacizumab is highly sensitive in pancreatic, breast and lung cancer models, detecting tumours earlier than 18FDG, with much better contrast between the tumour and the surrounding tissue and with fewer non-tumour-related hot spots. Because it uses different biological mechanisms compared with 18FDG, it could detect a broader range of tumour types than 18FDG.

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"Since bevacizumab has been approved by the FDA for treating patients and Copper-64 for clinical trials, the conjugated compound has a much higher chance of being applied to clinical use faster than other, newly developed bimolecular compounds.

"VEGF-related angiogenesis is almost a universal phenomenon for most types of solid tumours. We are testing this probe in different cancers (lung, pancreatic, ovarian, prostate, breast, and colon cancer) and bone metastasis models to verify our assumption. Once it's been verified and validated, we are planning to test it in clinical trials."

Dr Wang and his group are the first to show that it is possible to use bevacizumab as a diagnostic imaging agent to detect early tumours in animal models and that it is better than the gold standard 18FDG. However, he said that when he and his colleagues first started the project, some scientists and doctors in the cancer field did not believe their idea could work because VEGF is diffusible and breaks down very quickly. "They highly doubted the research goal and some of them refused to believe the first imaging result, which was thought too good to be true," he said.

The group persisted, and last year, another research group in The Netherlands independently published similar results in an ovarian tumour model. "Eventually we found out that while some types of VEGF are diffusible, other types of VEGF are located at the tumour cell surface and very near the extra cellular matrix. That is why the radiolabeled bevacizumab targets VEGF on the angiogenesis site around the tumour and demonstrates excellent imaging of the tumour. Since we are targeting early stage of angiogenesis we are able to see the tumour when it is still very small or in other words, in a very early stage."

Once researchers have obtained the necessary confirmation of their results in further studies and clinical trials, imaging with 64Cu-bevacizumab could be used in both pre-clinical and clinical work.

Dr Wang said: "In pre-clinical research it could be used for the following:

1) *Tumour detection*
   It could help researchers detect and observe the growth of the tumours located at greater depth in the body and offers better sensitivity and contrast.
2) *Estimate the tumour size and monitor the therapeutic effect*
   According to our results, bevacizumab imaging offers clearer contours of the tumours than other probes. With appropriate image analysis and experiment design, it could help researchers estimate the size of the tumour and further monitor the therapeutic effect of certain treatments.
3) *Observe angiogenesis-related events*
   The release of VEGF is highly related to angiogenesis. This compound can provide information about the distribution and the change of VEGF at different time points. Furthermore, this information can be used for evaluation of the functional effect of other anti-angiogenesis drugs. Also, it can tell the researcher which part of the tumour is actively undergoing angiogenesis at certain time point. VEGF is related to hypoxia and inflammation as well. Therefore, this probe may be used to obtain indirect information of hypoxia and inflammation.
4) *The pharmacokinetics and distribution of bevacizumab itself and other anti-cancer antibodies*
   It could offer information on the percentage of the total injection dose of bevacizumab accumulated in the tumour, also for other organs. The distribution of bevacizumab in the tumour could be revealed by this technique. All the imaging information is important for using bevacizumab more accurately and to optimise the drug dosing. The same imaging strategy can be used to evaluate the pharmacokinetics and distribution of other anti-cancer antibody candidates.

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"In clinical work with patients, the superior imaging will enable us to detect and diagnose tumours at earlier stages, to monitor the effects of therapy on the patients' cancers, and, because the contour of tumour is so much clearer with 64Cu-bevacizumab, it will help physicians to decide the size of the tumour and may be able to help the radiation oncologist decide the clinical treatment volume."

He said it was possible that other, targeted cancer therapies could be used for imaging in a similar way, but this depended on the type, biological distribution, specificity, and pharmacokinetics of the drug. "Some targeted drugs may be too specific to be used as the first-line imaging agent for the diagnosis of a broad spectrum of cancers. However, once the cancer is detected by the first-line imaging agent, other targeted cancer therapies may be useful as imaging agents when monitoring whether the drugs are sufficiently targeted at the tumour site. This will offer valuable information in deciding treatment strategy, such as dosing optimisation and personalised medicine."

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Abstract no: 33, oral presentation in plenary session 2, Room ABC, 15.00-16.00 hrs Wednesday 22 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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