# Nanotechnology advances brain cancer detection and therapy

Brain cancer is one of the most aggressive and lethal of malignancies, made even more difficult to treat by the fact that most anticancer drugs have a hard time even getting to the tumours.

Now, studies by three different groups of researchers show that targeted nanoparticles hold promise for solving this delivery problem.

In a report published in the journal *Small*, a team of investigators led by Miqin Zhang, Ph.D., principal investigator (PI) of the Nanotechnology Platform for Paediatric Brain Cancer Imaging and Therapy at the University of Washington, and Jim Olson, M.D., of the Fred Hutchinson Cancer Research Centre, describes its development of an iron oxide nanoparticle targeted to glioblastoma cells and shows that brain tumours in animal models take up these nanoparticles. The researchers start with iron oxide nanoparticles coated with PEG and add a targeting molecule known as chlorotoxin. Chlorotoxin is a peptide isolated from scorpions and has been shown to have high selectivity for binding strongly to gliomas and other malignancies, including prostate cancer, sarcoma, and intestinal cancer.

The investigators first tested this nanoparticle construct in glioma cells growing in culture, showing that the nanoparticle was internalised rapidly. More importantly, the nanoparticles ended up in the cells' cytoplasm rather than remaining confined within uptake vesicles known as endosomes. In contrast, nanoparticles lacking chlorotoxin showed almost no uptake by glioma cells. The researchers also showed in these experiments that they could detect the internalized nanoparticles using magnetic resonance imaging (MRI).

## Tumours soon apparent

Based on these results, the investigators examined whether these nanoparticles would target gliomas implanted in mice. By three hours after injection, tumours were readily apparent in MRI scans and were easily distinguished from surrounding healthy tissue. The researchers also found that maximal signal enhancement occurred approximately 12 hours after injection. A thorough examination of tissues from kidney, liver, and spleen showed no signs of acute toxicity from the nanoparticles.

In a second paper, published in the journal *Biomaterials*, Victor Yang, Ph.D., and colleagues at the University of Michigan showed that they could use a magnetic field to target iron oxide nanoparticles to gliomas implanted in the brains of mice. In this study, the investigators used commercially available iron oxide nanoparticles coated with starch. After placing tumour-bearing animals so that their heads rested between the poles of an electromagnet, the researchers injected nanoparticles into the animals' tail veins. After 30 minutes, the researchers then placed the animals into a small-bore MRI system. MRI

scans obtained 1 and 3 hours after injection showed significant accumulation of the nanoparticles within the tumours.

Shin-Ichi Miyatake, M.D., Ph.D., of Osaka Medical College in Japan led another team of investigators that developed a tumour-targeted liposome that was able to deliver high concentrations of boron to brain tumours for boron-neutron capture therapy, which in turn enhanced the survival of animals with implanted human brain tumours. They created the delivery vehicle first by forming PEG-coated liposomes loaded with sodium borocaptate and then attaching transferrin, a well-studied tumour-targeting agent, to the PEG coating. Researchers then loaded boron into liposomes coated with PEG.

## Lethal to the cells

Studies using glioma cells growing in culture showed that liposomes were internalised within 12 hours, concentrating in the cell nucleus. Neutron irradiation was lethal to the cells. In contrast, little effect was seen when cells were treated with an untargeted liposome or a targeted liposome lacking boron prior to neutron irradiation.

The researchers then injected the targeted liposomes into mice with tumours growing on one side of their brains. Boron accumulated in the tumours within 6 hours and remained there for at least 72 hours after administration, whereas very little boron accumulated in the opposite brain hemisphere. Neutron irradiation produced a marked effect on the treated animals, significantly increasing the time of survival.

The work from Drs. Zhang and Olson and their colleagues is detailed in the paper *In vivo MRI detection of gliomas by chlorotoxin-conjugated superparamagnetic nanoprobes.* This work was funded by the NCI's Alliance for Nanotechnology in Cancer. An investigator from the Children's National Medical Center in Washington, DC, also participated in this study. An abstract of this paper is available through PubMed.

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The work from Dr. Yang and collaborators is described in the paper *Iron oxide nanoparticles as a drug delivery vehicle for MRI monitored magnetic targeting of brain tumours.* This research was funded by the NCI. Investigators from chemicell GmbH in Berlin, Germany and from Tianjin University in China also participated in this study. An abstract of this paper is available through PubMed.

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The work from Dr. Miyatake and colleagues appears in the paper "Tumour-specific targeting of sodium borocaptate (BSH) to malignant glioma by transferrin-PEG liposomes: a modality for boron neutron capture therapy." Investigators from Hiroshima International University, Teikyo University, the Japan Atomic Energy Research Institute, and Kyoto University, all in Japan, also participated in this study. An abstract of this paper is available through PubMed.

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