Selective Peptidic Human Y₁ Agonist for BNCT
Carborane Conjugates for Boron Neutron Capture Therapy (BNCT) of Breast Cancer

**BACKGROUND/MEDICAL PROBLEM**

Boron neutron capture therapy (BNCT) allows the non-invasive treatment of cancer on a cellular level by cell specific elimination of malignant cells. The success of BNCT mostly depends on the quality of the boron delivery agent: It must deliver a high amount of boron into cancer cells with only low uptake of the compound in the surrounding healthy tissue. To achieve sufficient results, a very selective boron accumulation in the tumor is needed. One approach to this issue is the use of boron-modified peptide ligands that target distinct G protein-coupled receptors (GPCRs). A promising target GPCR for this purpose is the human Y₁ receptor (hY₁R), which is part of the four-membered Y-receptor family in humans and is activated by the natural ligand neuropeptide Y. Expression of the hY₁R was found in different cancer cells, including breast carcinoma (very high density in 65 % of tested breast tumors), adrenal gland and related tumors, renal cell carcinoma and ovarian cancer.

**IDEA**

Selective cell-targeting of breast tumors for BNCT by combining a specifically binding peptide bearing carboranes for high boron loading

**DEMONSTRATOR**

Activation of the human Y₁ receptor, resulting in internalization of the receptor into HEK293 cells transfected with the human Y₁R; no toxicity found up to 10 µM

**PROTOTYPE**

Successful targeting of the hY₁R in breast tumors in vivo has been shown by PET imaging in mice and by whole-body scintimammography in tumor patients; animal studies with hY₁R-carborane in preparation

**POTENTIAL APPLICATION**

- Non-invasive BNCT treatment of breast tumors, adrenal gland and related tumors, renal cell carcinoma and ovarian cancer

**ADVANTAGES**

- Treatment of early metastasis and resistant tumor cells
- Selective delivery of therapeutic agents into breast cancer cells
- High accumulation of boron in hY₁R receptor expressing cells
- Compounds can be converted to pharmaceutically acceptable salt
TECHNOLOGY/SOLUTION

To create novel BNCT agents for breast cancer targeting we combined hY₁R-selective NPY with carboranes for high boron loading. Carboranes are physiologically stable, hydrophobic and icosahedral carbon containing boron clusters. The compounds mediated effectively the activation of the human hY₁R, resulting in internalization of the receptor together with the compounds bonded to it, into HEK 293 cells transfected with the human Y₁ receptor. Furthermore, high levels of receptor activation and internalization are maintained over a range of carborane loadings (up to at least eight carborane units per peptide unit) enabling for transferring a large number of boron atoms per cell into cells expressing hY₁R. The good activation potency of the NPY conjugates on their capability to activate the hY₁ and hY₂ receptor was shown with an inositol phosphate accumulation assay in COS cells stably transfected with hY₁R or hY₂R and a chimeric G-protein. In addition, co-localization of fluorophore-labeled conjugates with the hY₁R in intracellular vesicles proved the receptor-mediated internalization of this carborane-containing conjugates.

STATUS OF PROPRIETARY RIGHTS

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COOPERATION OPTIONS

- License Agreement
- R&D Agreement
- Ownership Agreement

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