UNIVERSITÄT LEIPZIG

Selective Peptidic Human Y_1 Agonist for BNCT

Carborane Conjugates for Boron Neutron Capture Therapy (BNCT) of Breast 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 Y_1R; no toxicity found up to 10 µM

PROTOTYPE

Successful targeting of the hY_1R in breast tumors *in vivo* has been shown by PET imaging in mice and by whole-body scintimammography in tumor patients; animal studies with hY_1R-carborane in preparation

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 Y_1 receptor (hY_1R), which is part of the four-membered Y-receptor family in humans and is activated by the natural ligand neuropeptide Y. Expression of the hY_1R 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.

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 hY_1R receptor expressing cells
- Compounds can be converted to pharmaceutically acceptable salt

Project 19003

TECHNOLOGY OFFER

Picture: Colourbox

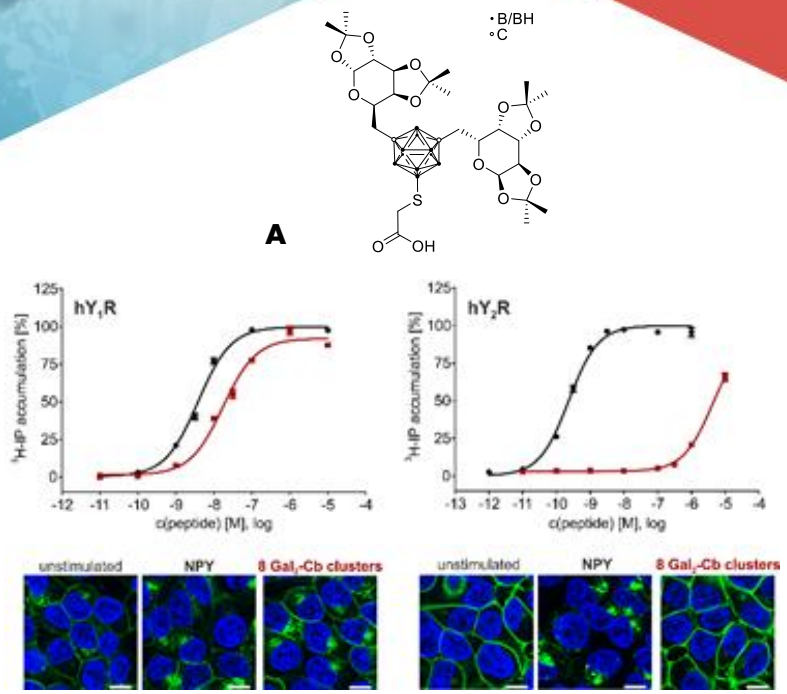

Figure
A Saccharide functionalized carborane derivative.
B Selective signal transduction and internalization of a neuropeptide Y conjugate modified with eight Gal_2-Cb clusters.

TECHNOLOGY/SOLUTION

To create novel BNCT agents for breast cancer targeting we combined hY_1R-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 hY_1R, resulting in internalization of the receptor together with the compounds bonded to it, into HEK 293 cells transfected with the human Y_1 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 hY_1R. The good activation potency of the NPY conjugates on their capability to activate the hY_1 and hY_2 receptor was shown with an inositol phosphate accumulation assay in COS cells stably transfected with hY_1R or hY_2R and a chimeric G-protein. In addition, co-localization of fluorophore-labeled conjugates with the hY_1R in intracellular vesicles proved the receptor-mediated internalization of this carborane-containing conjugates.

FURTHER READING

Ahrens et al., *ChemMedChem* 2015, 10, 164–172
(DOI: 10.1002/cmdc.201402368)

Böhme et al., *ChemMedChem* 2015, 10, 804–814
(DOI: 10.1002/cmdc.201402514)

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(DOI: 10.1016/j.poly.2012.03.003)

Frank et al., *J. Organomet. Chem.* 2015, 798, 46–50
(DOI: 10.1016/j.jorganchem.2015.08.011)

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- License Agreement
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