UNIVERSITÄT LEIPZIG

Selective Ghrelin Receptor Agonist for BNCT

Carborane Conjugates for Boron Neutron Capture Therapy (BNCT) of Pituitary, Prostate, Endometrium and 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 and internalization studies;
Chemical stability test in Water/Acetonitrile

PROTOTYPE

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). The ghrelin receptor (GHSR) was found to be expressed in tumors including pituitary, prostate, endometrium and breast cancer. Thus, addressing the receptor with peptides binding to the receptor is a promising approach for selective tumor targeting. Most preferable are highly potent agonists that internalize together with the receptor and thereby, act as a shuttle system.

POTENTIAL APPLICATION

- Non-invasive BNCT treatment of pituitary, prostate, endometrium and breast cancer

ADVANTAGES

- Highly specific peptidic human ghrelin receptor agonist
- High accumulation of boron in hGHSR expressing cells
- Biologically stable
- Compounds can be converted to pharmaceutically acceptable salt

Project 19004

TECHNOLOGY OFFER

Picture: Colourbox

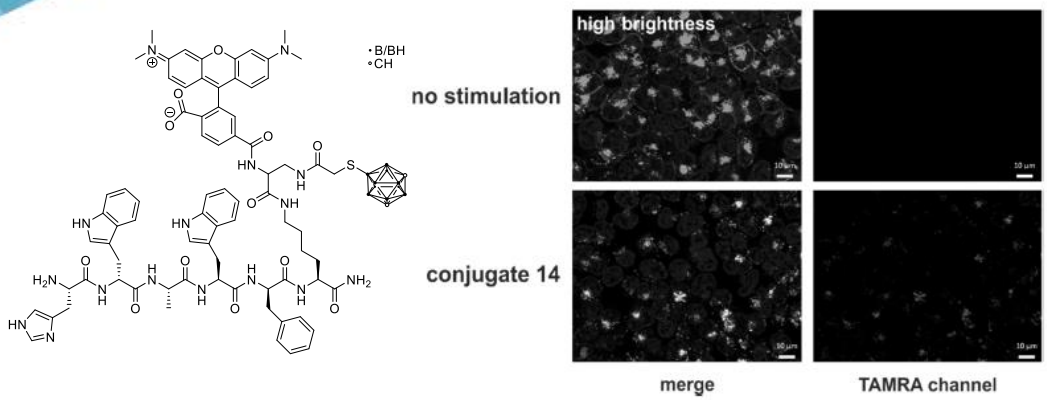

Figure
A Peptidic human Ghrelin receptor agonist functionalized with *meta*-carborane derivative to prepare conjugate 14.
B Uptake of conjugate 14 into GHSR-expressing cells. After starving for 30 min, HEK239_GHSR1a_eYFP cells were stimulated with 100 nM conjugate 14 for 1 h at 37 °C. Scale bar = 10 µm.

TECHNOLOGY/SOLUTION

Therefore we designed an high effective peptidic agonists for the ghrelin receptor and combined this peptides with carboranes for high boron loading to create novel BNCT agents. Carboranes are physiologically stable, hydrophobic and icosahedral carbon containing boron clusters. Activation of the ghrelin receptor (GHSR) by the carborane-modified agonists was shown in an inositol phosphate accumulation assay. One compound was found to be a superagonist for the GHSR, with nanomolar potency and a higher maximal receptor activation than Ghrelin. The compounds mediated effectively the activation of the human GHSR, resulting in internalization of the receptor together with the compounds bonded to it, into HEK 293 cells transfected with the human GHSR. In addition , co-localization of fluorophore-labeled conjugates with the hGHSR in intracellular vesicles proved the receptor-mediated internalization of this carborane-conjugates.

FURTHER READING

Sivertsen et al, *J Biol Chem* 2011, 286, 20845
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(DOI: 10.1016/j.jorganchem.2015.08.011)

STATUS OF PROPRIETARY RIGHTS

WO 2019/ 115624 A1,
positive search report

COOPERATION OPTIONS

- R&D Agreement
- License Agreement
- Ownership Agreement

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