UNIVERSITÄT LEIPZIG

Peptidic Melanocortin 1 Agonist for BNCT

Carborane Conjugates for Boron Neutron Capture Therapy (BNCT) of Melanoma

IDEA

Selective cell-targeting of primary and metastatic melanomas for BNCT by combining a specifically binding peptide bearing carboranes for high boron loading

DEMONSTRATOR

Activation of the human melanocortin 1 receptor (MC1R), resulting in internalization of the receptor into HEK293 cells transfected with the human MC1R.

PROTOTYPE

In preparation

BACKGROUND/ MEDICAL PROBLEM

The main reason for the deadliness of malignant melanoma, which is responsible for over 10,000 deaths every year solely in the United States, is its spreading to other tissues *via* infiltration of the blood or lymphatic system. In addition, the treatment of this cancer type is difficult due to early metastasis and resistance of the disseminated cells towards state of the art therapies. Boron neutron capture therapy (BNCT) could be an alternative to the traditional radiation-, chemo-therapy or surgery. BNCT allows the non-invasive treatment of cancer on a cellular level by cell specific elimination of malignant cells. To achieve sufficient results, a very selective boron accumulation in the tumor is needed but so far there's no selective cell-targeting compound on the market. One very promising receptor for selective cell-targeting is the MC1R. It is a G-protein-coupled receptor, which shows strong expression in primary and metas-tatic melanomas.

POTENTIAL APPLICATION

- Non-invasive BNCT treatment of malignant melanomas

ADVANTAGES

- Treatment of early metastasis and resistant tumor cells
- Highly specific peptidic MC1R agonist
- High accumulation of boron in MC1R expressing cells
- Compounds can be converted to pharmaceutically acceptable salt

Project 19002

TECHNOLOGY OFFER

Picture: Colourbox

TECHNOLOGY/SOLUTION

Therefore we combined the highly selective binding octapeptide NAPamide, a synthetic, shortened and modified derivative of the endogenous MC1R ligand α-MSH (α-melanocyte stimulating hormone) 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 MC1R, resulting in internalization of the receptor into HEK293 cells transfected with the human MC1R. They can therefore be used to selectively transport boron atoms into cells expressing the MC1R, such as melanoma cells, to enable boron neutron capture therapy. Furthermore, high levels of receptor activation and internalization are maintained over a range of carborane loadings (up to at least four carborane units per peptide unit) enabling for transferring a large number of boron atoms per cell into cells expressing the human MC1R.

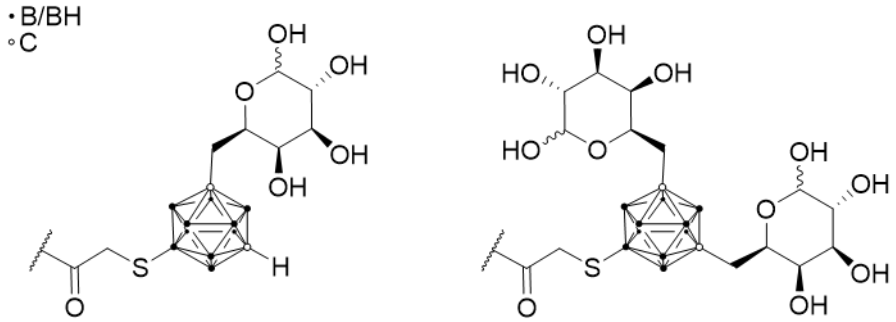

Figure
Two saccharide modified *meta*-carborane fragments are depicted which could be attached to the MC1R agonist.

FURTHER READING

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

Frank et al., *Polyhedron* 2012, 39, 9–13 (DOI: 10.1016/j.po.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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COOPERATION OPTIONS

- R&D Agreement
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