Selective $BB_2$ Receptor Agonist for BNCT
Carborane Conjugates for Boron Neutron Capture Therapy (BNCT) of Breast, Prostate and Small-cell Lung Cancer

**BACKGROUND/MEDICAL PROBLEM**
Since cancers of the breast, prostate and the lung are amongst the most common cancers in women and men worldwide, there is a substantial need for treatment and boron neutron capture therapy (BNCT) could be an alternative to the traditional radiation-, chemotherapy or surgery. BNCT allows the non-invasive treatment of cancer on a cellular level by cell specific elimination of malignant cells. Requirement for this binary approach is the administration of a tumor-seeking drug containing a non-radioactive isotope with a high neutron cross section. Following this, the tumor will be irradiated locally with low energy neutrons that induce a nuclear fission reaction. The excited $^{11}$B* nuclides are instable and decompose in high linear energy transfer (LET) $^4$He and $^7$Li particles. Due to limited path lengths of the particles in tissue ($5-9 \mu m$), the destructive effects of those is limited to boron containing cells. To achieve sufficient results, a very selective boron accumulation of $5-20 \mu g/g$ tumor is needed.

**ADVANTAGES**
- Non-invasive BNCT treatment of prostate-, breast- and small-cell lung cancer
- Highly specific peptidic $BB_2$ receptor agonists (up to sixteen carborane units per peptide unit)
- High accumulation of boron in $BB_2$ receptor expressing cells
- Compounds can be converted to pharmaceutically acceptable salts

**POTENTIAL APPLICATION**
- Non-invasive BNCT treatment of prostate-, breast- and small-cell lung cancer

**IDEA**
Selective cell-targeting of breast, prostate and small-cell lung tumors for BNCT by combining a specifically peptidic human $BB_2$ receptor agonist bearing carboranes for high boron loading

**DEMONSTRATOR**
Activation of the human $BB_2$ receptor, resulting in internalization of the receptor into HEK293 cells transfected with the human $BB_2$ receptor

**PROTOTYPE**
In preparation

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One very promising receptor to be addressed is the gastrin releasing peptide receptor (BB₂, GRPR). It is part of the bombesin receptor family consisting of three G protein-coupled receptors (BB₁; BB₂; BB₃) widely expressed in brain and peripheral tissues. BB₂-receptor is significantly overexpressed in prostate- and breast cancer tissues.

We therefore generated highly selective peptide drug conjugates, which are modified with carboranes. Carboranes are boron clusters that consist of ten boron and two carbon atoms. They are stable under biological conditions. All compounds showed great receptor activation efficacy. Even the compounds with the highest boron loading (up to sixteen carborane units per peptide unit) were effectively internalized into HEK293 cells expressing the BB₂ receptor.

FURTHER READING:

[DOI: 10.2174/187152008783497046]

Frank et al., Polyhedron 2012, 39, 9-13  
[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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Figure

A Saccharide functionalized meta-carborane derivatives as boron-rich coupling partners for the selective BB₂ receptor agonist.

B Selective signal transduction and internalization of a selective bombesin derivative modified with eight Gal₂-Cb clusters.