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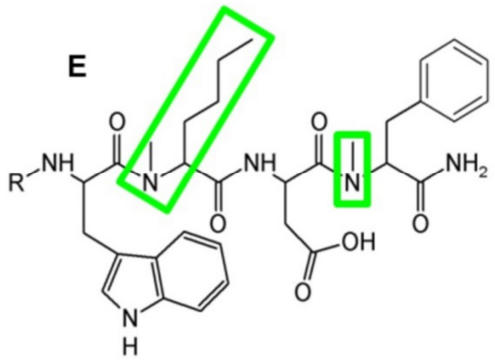
Stabilized minigastrin analogs for enhanced CCK2R targeting and applications in neuroendocrine tumor therapeutics and diagnostics

Reference Number TO 42-00022

Challenge

An attractive target for different tumors, especially neuroendocrine tumors like medullary thyroid carcinoma (MTC) and small cell lung cancers (SCLC) has been identified in the cholecystokinin-2 receptor (CCK2R). CCK2R is overexpressed in different neoplasms, however, targeting CCK2R with natural ligands minigastrin and cholecystokinin did not result in a successful therapeutic application. Many attempts have been made to find CCK2R specific targeting ligands suitable for single photon emission tomography (SPECT), positron emission tomography (PET), and therapeutic applications using radiolabeled peptides. Different radiolabeled peptides have been developed based on the endogenous ligands. However, short physiological half-life, low enzymatic stability, low bioavailability, and high uptake in kidneys, the latter leading to nephrotoxic side effects, are shortfalls in view of an effective therapeutic success.



Structure of minigastrin analog DOTA-MGS4, R means DOTA-D-Glu-Ala-Tyr-Gly (source: PD Dr. von Guggenberg)

Technology

To address these problems and to provide an effective therapeutic as well as diagnostic approach in targeting neuroendocrine tumors, different modifications of the peptide sequence of minigastrin analogs have been investigated. These especially included site-specific chemical modifications at the C-terminal receptor-binding part of the peptide. Substitution of Met against unnatural N-methylated (N-Me) norleucin (Nle) and substitution of Phe against 1-naphthylalanine (1-Nal) or (N-Me)Phe (marked in Figure aside) lead to a high stability of the metal complex in ^{111}In-labelled and ^{177}Lu-labelled DOTA-peptides against enzymatic degradation *in vitro* and *in vivo*. Due to this improved bioavailability, the peptide analogs showed retained and high receptor affinity and higher tumor cell uptake with reduced uptake in stomach and kidney in a xenograft mouse model. In small animal NanoSpect/CT imaging studies, a favorable distribution with reduced kidney uptake was found leading to high-contrast imaging.

Commercial Opportunity

It could be demonstrated that minigastrin analogs can be stabilized against enzymatic degradation *in vivo* without losing CCK2R affinity. This not only leads to minigastrin analogs with improved bioavailability, but more importantly significantly increases tumor uptake. Thus, the minigastrin analogs seem most suitable for CCK2R targeting and theranostic use with alternative radionuclides.
The technology is open for licensing, further co-development is highly welcomed.

Developmental Status

For radiolabeling with ^{68}Ga, a kit formulation has been developed allowing the standardized preparation of the radiopharmaceutical in the clinical setting. For further clinical translation, GMP material needs to be provided and an extended single dose toxicity study in rodents needs to be performed.

Patent Situation

A PCT patent application has been filed in June 2018 (priority June 2017).

Further Reading

Klingler et al. (2018), Theranostics 8:2896-2908; Rangger et al. (2017), Mol. Pharm. 14:3045-3058

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