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Primary Contact:
Lurdes Gano, University of Lisbon, Instituto Superior Técnico
Bobadela, Portugal

All Authors:
Lurdes Gano, University of Lisbon, Instituto Superior Técnico **(Primary Presenter)**
Alice D'Onofrio, Instituto Superior Tecnico/CTN
Francisco Silva
Paula Dolores Raposinho, Instituto Superior Tecnico/CTN
Arkadiusz Sikora, National Centre for Nuclear Research Radioisotope Centre POLATOM
Monika Orzełowska, National Centre for Nuclear Research, Radioisotope Centre POLATOM
Renata Mikołajczak, National Centre for Nuclear Research, Radioisotope Centre POLATOM
Piotr Garnuszek, National Centre for Nuclear Research Radioisotope Centre POLATOM
António Paulo, Instituto Superior Tecnico/CTN

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Submission Category:
Radiotherapy and Radiotheragnostics

Title:

Bioorthogonal Chemistry Approach for Theranostics of GRPR-expressing Cancers

Abstract:

Objectives

Pre-targeted approaches based on the biorthogonal inverse-electron-demand Diels-Alder reaction between strained trans-cyclooctenes (TCO) and electron-deficient tetrazines (Tz), have emerged in recent years and have proven to be an effective in vivo alternative to classic targeted strategies by improving the targeting properties and the pharmacokinetics of radiolabelled molecules, mainly antibodies. Therefore, the aim of this study was the biological evaluation of clickable radiocomplexes to investigate the improvement of the pharmacokinetics of radiolabelled peptides for peptide radionuclide receptor therapy using a pre-targeting approach. To achieve this goal, we have explored the in vivo pre-targeting of gastrin-releasing peptide receptor (GRPR) using a clickable bombesin (BBN) antagonist (AR) and [^{111}In]DOTA-based clickable complexes.

Methods

A small family of tetrazine-containing DOTA-based clickable chelators used for labelling with medically relevant radiometals (e.g. ^{111}In) was synthesised. The in vivo stability and the pharmacokinetic profile of the [^{111}In]radiocomplexes was assessed by biodistribution studies in healthy CD-1 mice [1]. The biodistribution of the most promising [^{111}In]DOTA-Tz complex was then assessed in a human prostate tumour model in Balb-C nu/nu mice bearing PC3 xenografts. A BBN antagonist modified with two different clickable moieties were also synthesised. The binding affinities and the cellular uptake of the [^{111}In]radioconjugates were determined in PC3 prostate cancer cells. The in vivo click reaction of the [^{111}In]DOTA-Tz complex with the clickable derivatives (TCO-PEG4-AR and TCO-Pip-AR) and their ability to target the GRPR was tested in the tumour-bearing model. For that, the clickable derivatives were injected in the tumour-bearing mice followed by the radiocomplex [^{111}In]DOTA-Tz, and the mice were sacrificed at different post-injection times (p.i.).

Results

The clickable chelators were successfully used to prepare the ^{111}In-complexes with high specific activity, good radiochemical yields, high radiochemical purity and high stability. Biodistribution studies pointed out a short half-life in blood stream with no relevant uptake in any main organ or tumours, together with a very fast whole body radioactivity excretion. The TCO-AR derivatives were successfully used to obtain a [^{111}In]radioconjugate after click reaction with the radiocomplex [^{111}In]DOTA-Tz. The ^{111}In-DOTA-Tz-TCO-PEG4-AR displayed the highest cellular uptake in PC3 (GRPR+) cells that was inhibited by bombesin, the GRPR agonist. Analysis of a pilot biodistribution study was encouraging since a quick tumour uptake with a fast washout and no radioactivity accumulation in main organs, except those related with the urinary tract, were obtained.

Conclusions

The results of our in vivo studies are encouraging and provide evidence that the designed clickable complexes are useful for pre-targeting strategies using GRPR antagonists. However, the use of peptide antagonists for this purpose has been almost unexplored, as far as we are aware. Further research is needed to optimize the parameters involved in this pre-targeting strategy and assess its usefulness for future studies.

Acknowledgments

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References

[1] Alice D'Onofrio et al., *Frontiers in Medicine* **8**, 647379 (2021).

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