A Theranostic Application of Cobalt-55/58m

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Introduction
Targeted Radionuclide Therapy (TRT) with radiometals has shown promise for cancer treatment. Low-range, high linear energy transfer (LET) Auger electrons may avoid radiotoxicities associated with higher energy electrons used for radiotherapy with approved beta-emitting drugs (e.g., [177Lu]Lu-DOTA-TATE).  58mCo (t1/2 = 9.1h) emits Auger electrons and has suitable decay characteristics (99.96% IC) and forms stable complexes with clinically relevant chelators like NOTA and DOTA. Auger electron TRT benefits from nuclear localizations of the radionuclide, generating DNA double-strand breaks. The neurotensin molecule is a promising targeting vector for Auger electron TRT. Neurotensin receptors (NTSR1,2,3) stimulate tumor proliferation through neurotensin (NTS) activation and are expressed by a variety of cancers including breast, pancreatic, prostate, colon and non-small cell lung cancers. In addition to targeting many cancers, Auger electron-emitting radionuclides can directly benefit from the intracellular nuclear localization of NTS/NTSR1. However, the lack of positrons and higher energy photons make 58mCo-labeled complexes difficult to detect in vivo. Fortunately, 58mCo (t1/2 = 17.5h) can be used for positron emission tomography (PET) and serve as a surrogate for 58mCo to determine the pharmacokinetics. We investigated the radiopharmaceutical potential of [55,58mCo]Co-NOTA-NTS20.3 (an NT analog) with NTSR1-positive HT29 human colorectal adenocarcinoma cells.

Cyclotron Production of 55,58mCo at UW-Madison

8.2MeV Deuteron 54Fe (or 57Fe) on Ag backing

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4M HCl

4 M HCl

8M HCl

3M HCl

3 M HCl

8 M HCl

3 M HCl

Recycle 54Fe (or 57Fe)

Recycle 54Fe (or 57Fe)

HPLC Radiochemical Purity Assessment of [58mCo]Co-NOTA-NTS20.3 shows:
- >99% radiochemical purity at 0.2Ci/μmol
- No radioisolation after purification (dried to <10μL at 95°C under light Ar flow)
- >99% radiochemical purity after 12h in human serum

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In Vitro Cell Studies with HT29 Cells

[58mCo]Co-NOTA-NTS20.3 internalizes rapidly (>80% in 1h)

[58mCo]Co-NOTA-NTS20.3 is >15x cytotoxic than non-conjugated 58mCo

58mCo-NOTA-NTS20.3 revealed primarily kidney biodistribution

In vivo PET Imaging and Ex Vivo Biodistribution

Subcutaneously xenografted HT29 cells onto female athymic nude mouse then administered 130µCi (4.8MBq) of [58mCo]Co-NOTA-NTS20.3 2 weeks after

9h p.i. ex vivo bioD

We observed rapid internalization of [58mCo]Co-NOTA-NTS20.3 in NTSR1 positive HT29 cells with approximately 10% nuclear intracellular localization. [58mCo]Co-NOTA-NTS20.3 exhibited >15x increase in cytotoxicity as compared to free 58mCo, showing the impact of targeting vectors in Auger TRT. In vivo assessment of the pharmacokinetics of [58mCo]Co-NOTA-NTS20.3 revealed primarily kidney and tumor uptake and corroborated with ex vivo quantification. Given the favorable biodistribution profile and promising cytotoxicity data, [58mCo]Co-NOTA-NTS20.3 shows potential for Auger TRT and warrants further research.

Conclusions

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