A Theranostic Application of Cobalt-55/58m

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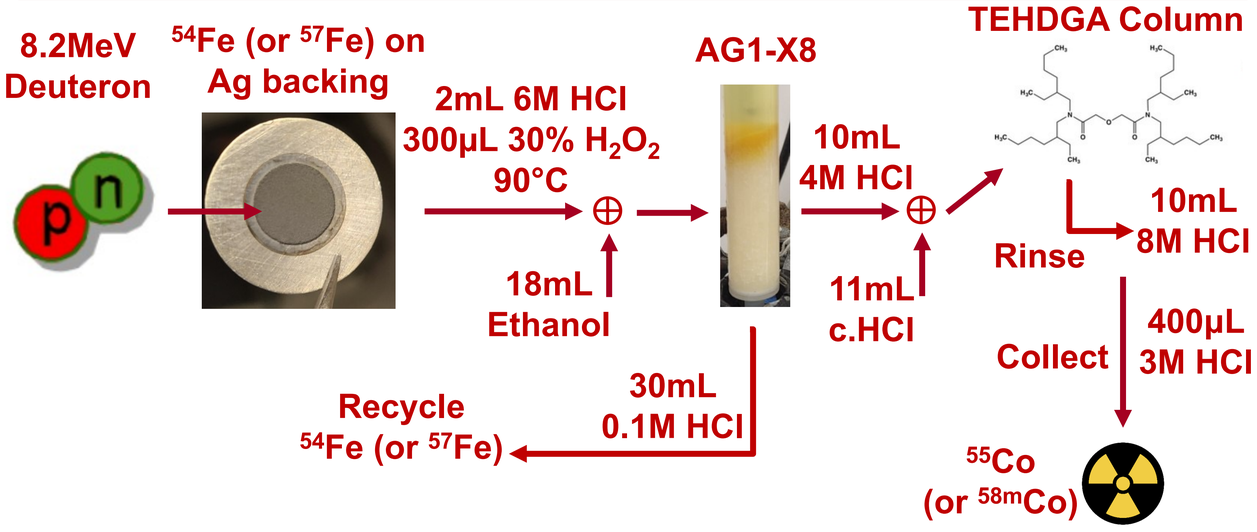
Introduction

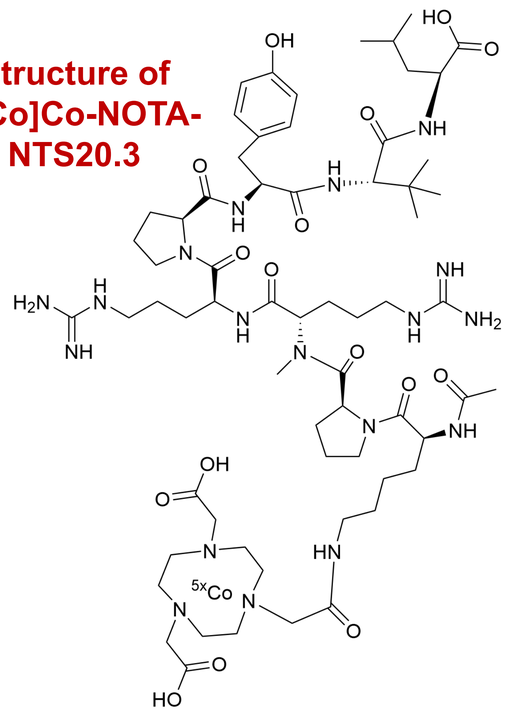
Targeted Radionuclide Therapy (TRT) with radiometals has shown promise for cancer treatment. Low-range, high linear energy transfer (LET) Auger electrons may avoid radiotoxicities associated with higher energy electrons used for radiotherapy with approved beta-emitting drugs (e.g., [^{177}Lu]Lu-DOTA-TATE). ^{58m}Co ($t_{1/2}$ =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 ^{58m}Co-labeled complexes difficult to detect *in vivo*. Fortunately, ^{55}Co ($t_{1/2}$ = 17.5h) can be used for positron emission tomography (PET) and serve as a surrogate for ^{58m}Co to determine the pharmacokinetics. We investigated the radiopharmaceutical potential of [^{55,58m}Co]Co-NOTA-NTS20.3 (an NT analog) with NTSR1-positive HT29 human colorectal adenocarcinoma cells.

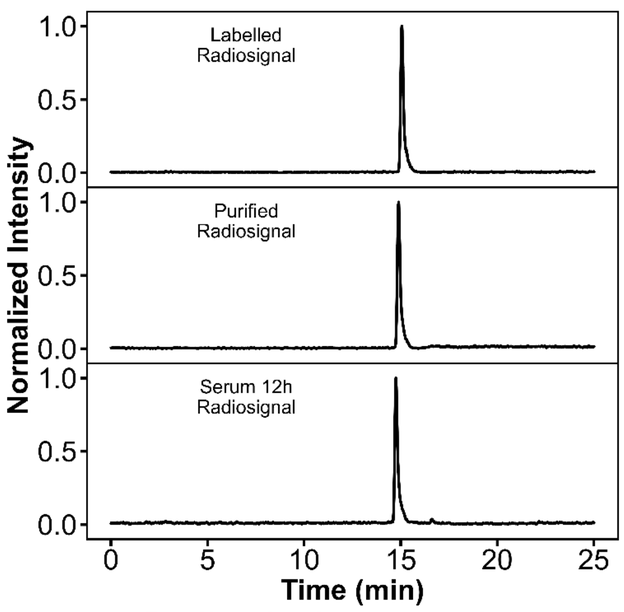
Cyclotron Production of ^{55,58m}Co at UW-Madison



Radiochemical Purity – Quality Control

Structure of [^{5x}Co]Co-NOTA-NTS20.3





Radiolabeling procedure:
pH4.5, 0.2Ci/µmol, 95°C, 1h
2mg/mL gentisic acid

HPLC Radiochemical Purity Assessment of [^{5x}Co]Co-NOTA-NTS20.3 shows:

- **>99% radiochemical purity at 0.2Ci/µmol**
- **No radiolysis after purification (dried to <10µL at 95°C under light Ar flow)**
- **>99% radiochemical purity after 12h in human serum**

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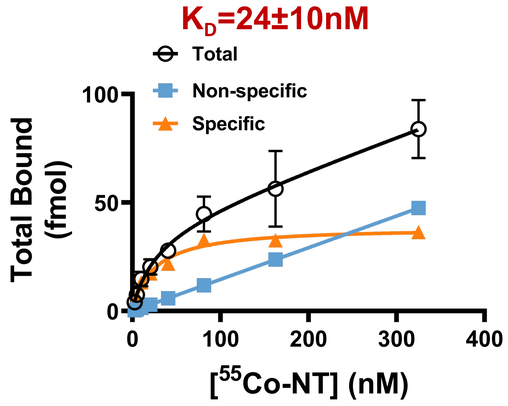
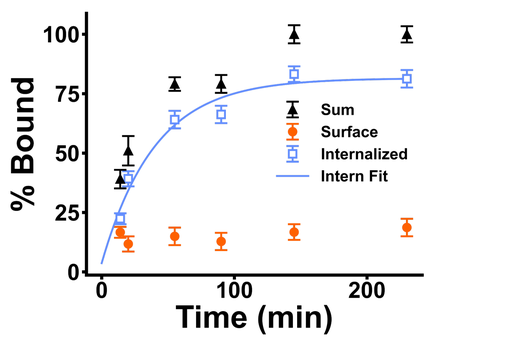
In Vitro Cell Studies with HT29 Cells

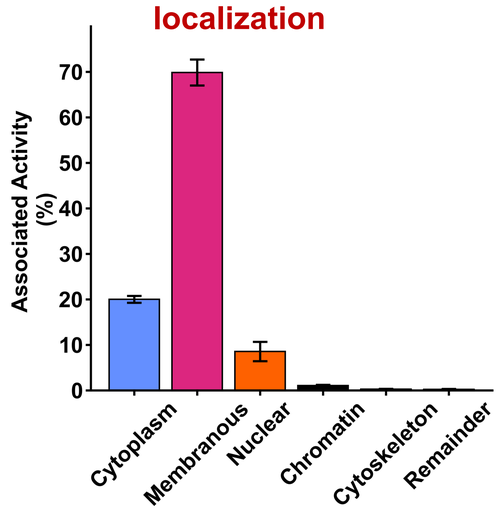
[^{55}Co]Co-NOTA-NTS20.3
K_D=24±10nM



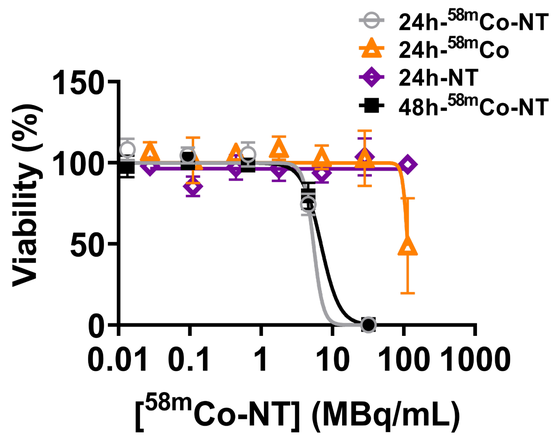
[^{55}Co]Co-NOTA-NTS20.3 internalizes rapidly (>80% in 1h)



~10% nuclear intracellular localization



[^{58m}Co]Co-NOTA-NTS20.3 is >15x cytotoxic than non-conjugated ^{58m}Co

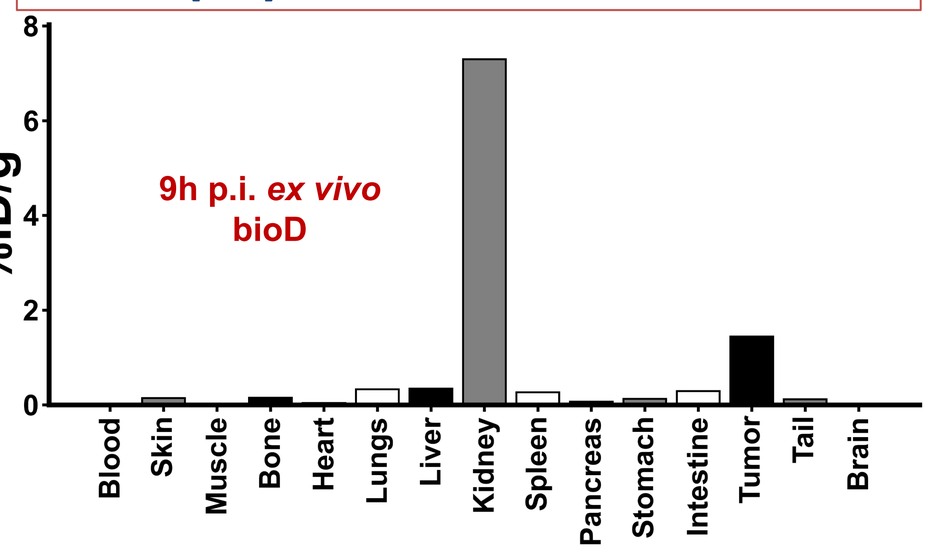


In vivo PET Imaging and *Ex Vivo* Biodistribution

9h p.i. microPET/CT MIP

Subcutaneously xenografted HT29 cells onto female athymic nude mouse then administered 130µCi (4.8MBq) of [^{55}Co]Co-NOTA-NTS20.3 2 weeks after

9h p.i. *ex vivo* bioD



Conclusions

We observed rapid internalization of [^{55}Co]Co-NOTA-NTS20.3 in NTSR1 positive HT29 cells with approximately 10% nuclear intracellular localization. [^{58m}Co]Co-NOTA-NTS20.3 exhibited >15x increase in cytotoxicity as compared to free ^{58m}Co, showing the impact of targeting vectors in Auger TRT. *In vivo* assessment of the pharmacokinetics of [^{55}Co]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, [^{58m}Co]Co-NOTA-NTS20.3 shows potential for Auger TRT and warrants further research.

Acknowledgements

We thank the Cancer Center Support Grant: NCI P30 CA014520, University of Wisconsin Small Animal Imaging & Radiotherapy Facility for supporting this work. We are grateful for the support from NIH/NCI award P01-CA250972. We thank Dr. Reinier Hernandez for the helpful discussions. We thank Dr. Jeanine Batterton for her assistance with HPIC analysis and Justin Jeffery for his technical assistance during the imaging experiments. This work was supported in part by Department of Energy Isotope Program's Grant DE-SC0022550, the Horizon-broadening Isotope Production Pipeline Opportunities (HIPPO) program.