

Decay induced de-chelation of positron-emitting electron-capture daughters and its use in preclinical PET.

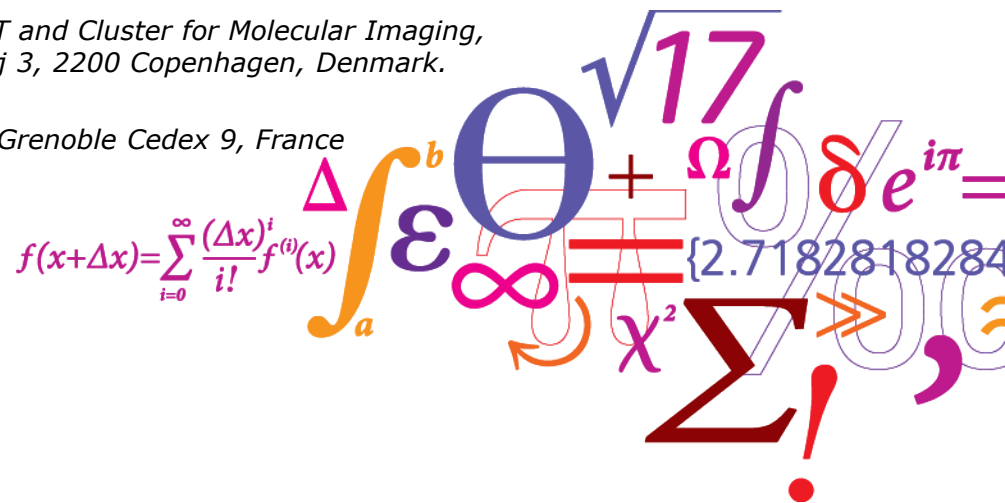
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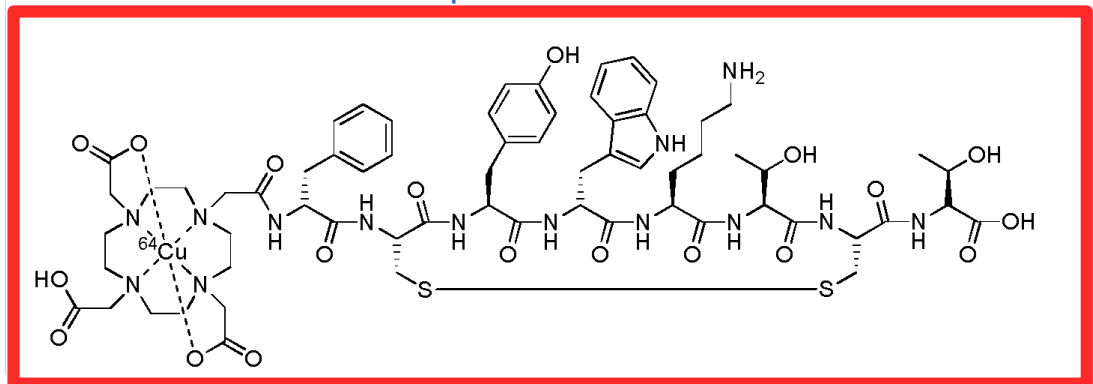


Receptor-based Positron Emission Tomography (PET)



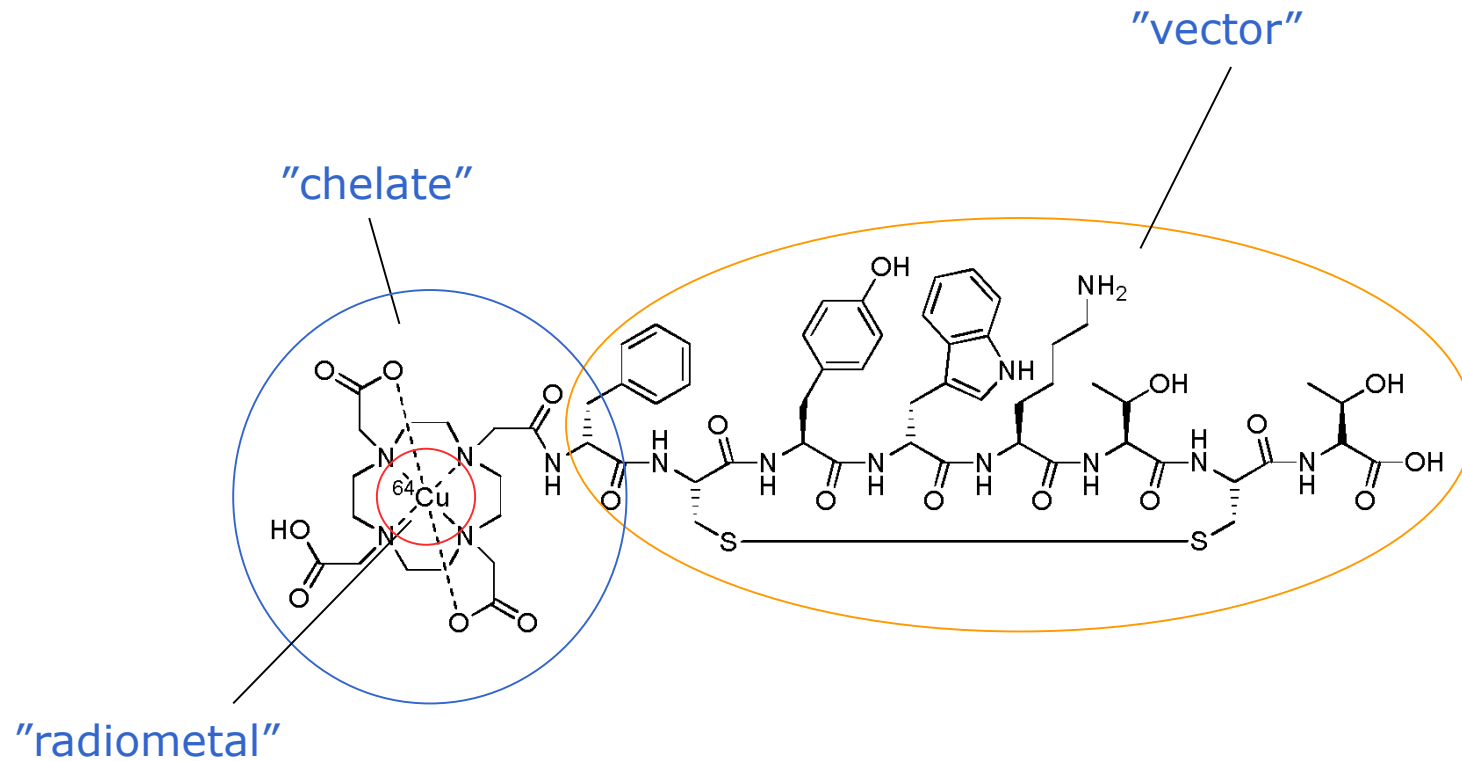
^{64}Cu -DOTATATE

- 3-dimensional quantifiable tomography
- Used primarily in medical diagnosis.
- non-invasive.
- Requires positron emitting radionuclides to be covalently bound to a targeting molecule(vector).
- Images like these compel a transition from diagnostics to therapeutics

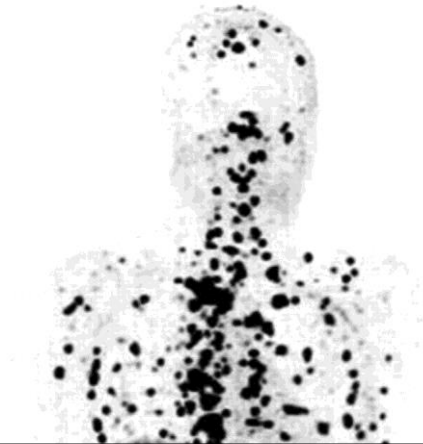


Pfiefer *et al.* J Nucl Med. 2012 Aug;53(8):1207-15

Language



Imaging-to-Therapy



- If we can find cancer can we also treat it using the same vectors?
- Use vectors for drug delivery-
- Drug-loaded nanoparticles
- Radionuclides

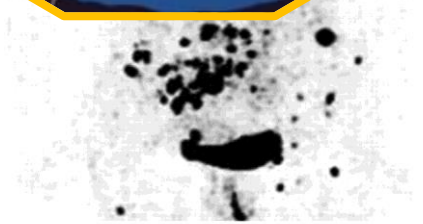
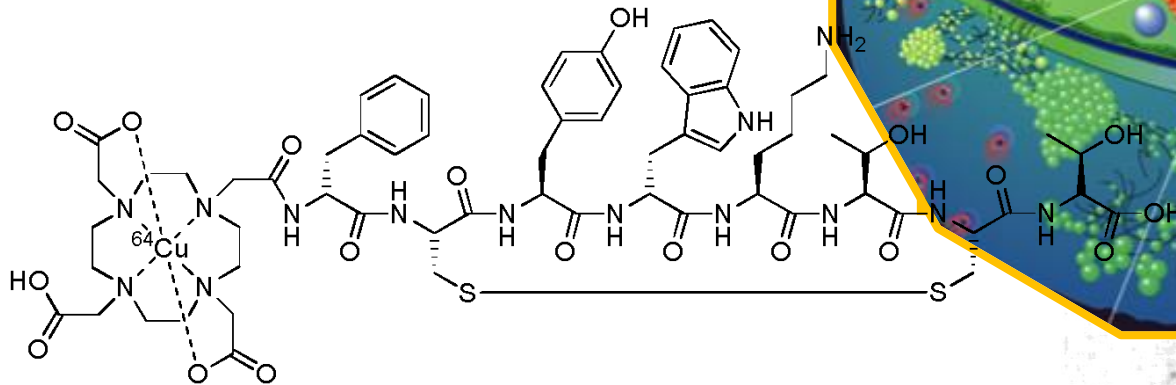
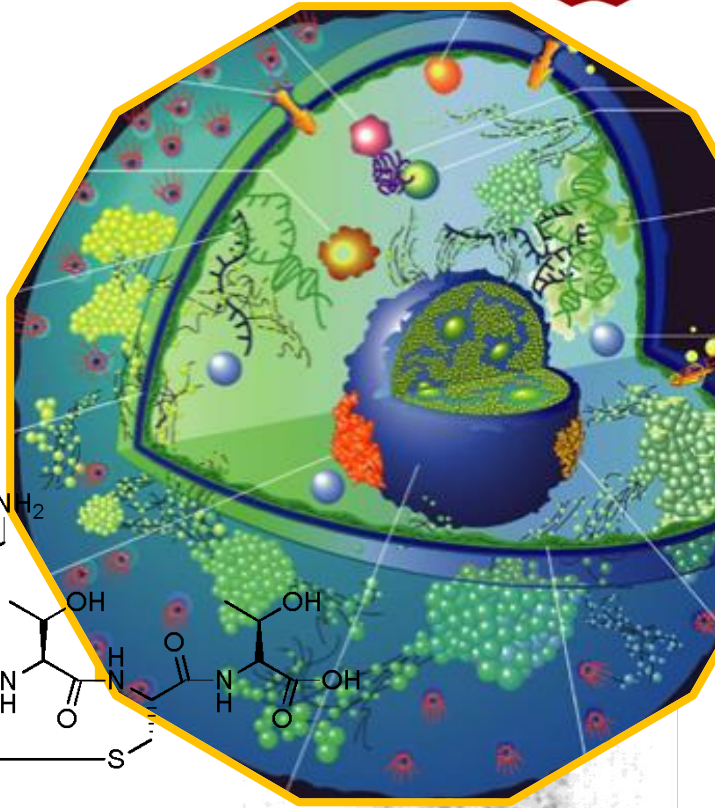
Can we make a PET technique to determine if therapeutic agents are internalized or not?



^{64}Cu -DOTATATE

Work best if 'internalized'

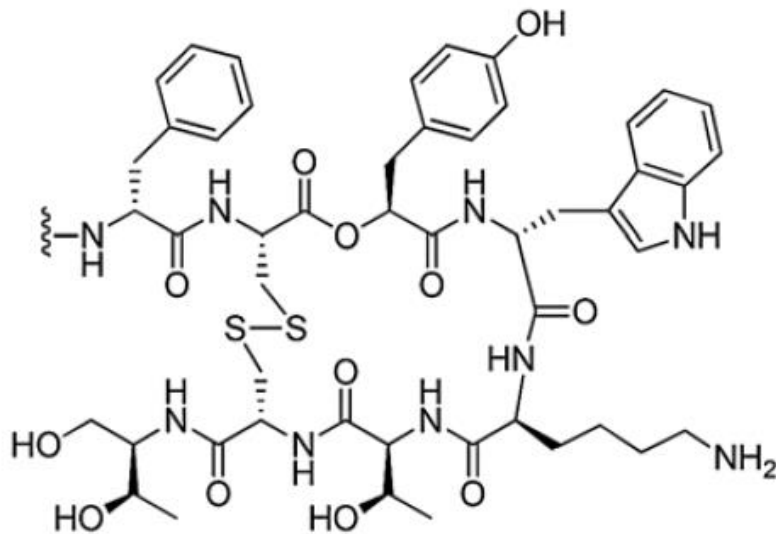
"Internalization"



^{64}Cu -DOTATATE

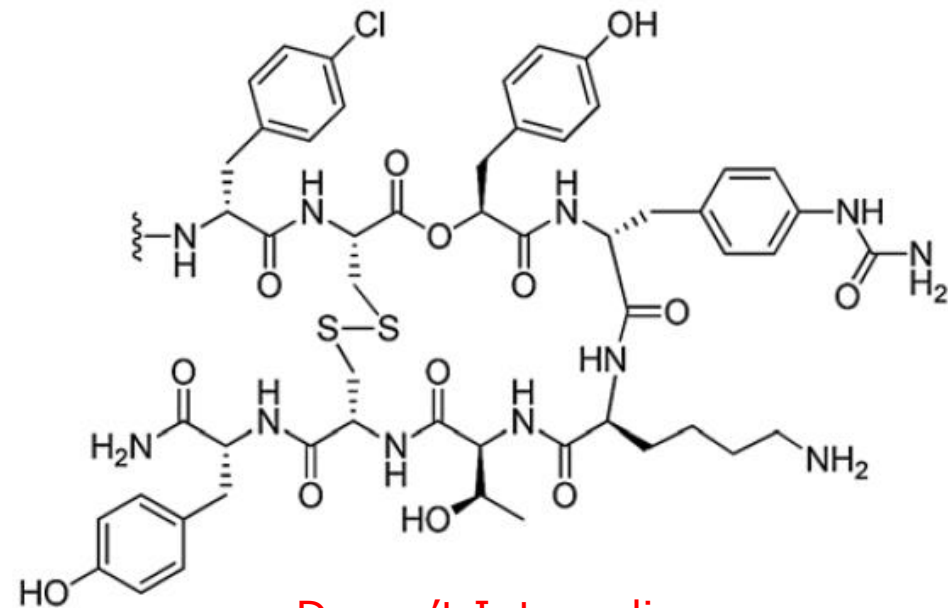
Small modifications change internalization status

(DOTA)TATE



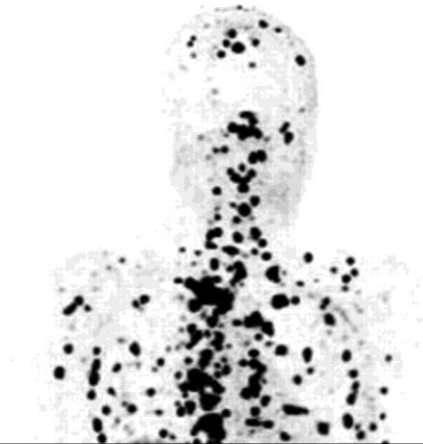
Internalizes

(DOTA)LM3



Doesn't Internalize

Imaging-to-Therapy



- If we can find cancer can we also treat it using the same vectors?
- Use vectors for drug delivery-
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- Radionuclides

Can we make a PET technique to determine if therapeutic agents are internalized or not?



^{64}Cu -DOTATATE

Work best if 'internalized'

Enter ISOLDE

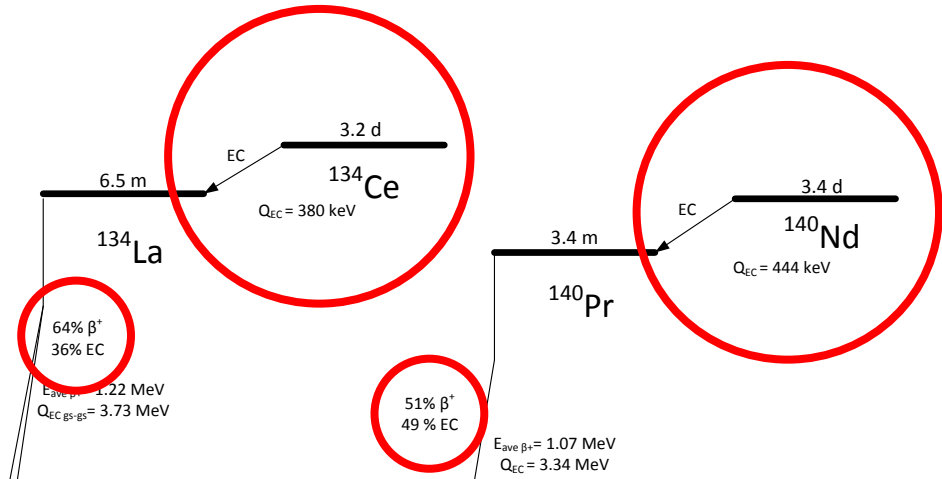
^{134}Ce and ^{140}Nd

Nearly identical decay schemes to 'short-lived' positron emitting daughters.

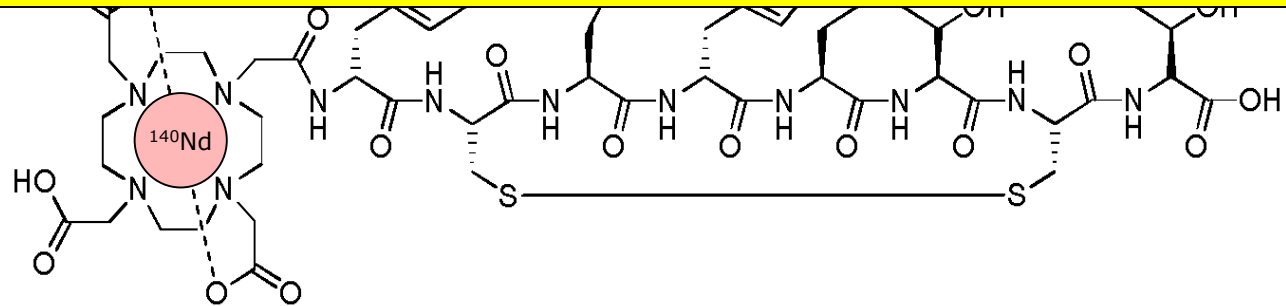
Nearly identical lanthanide chemistry

Difficult to purify, except at ISOLDE.

Match perfectly with DOTATATE



Electron Capture Decay is special, chemically.



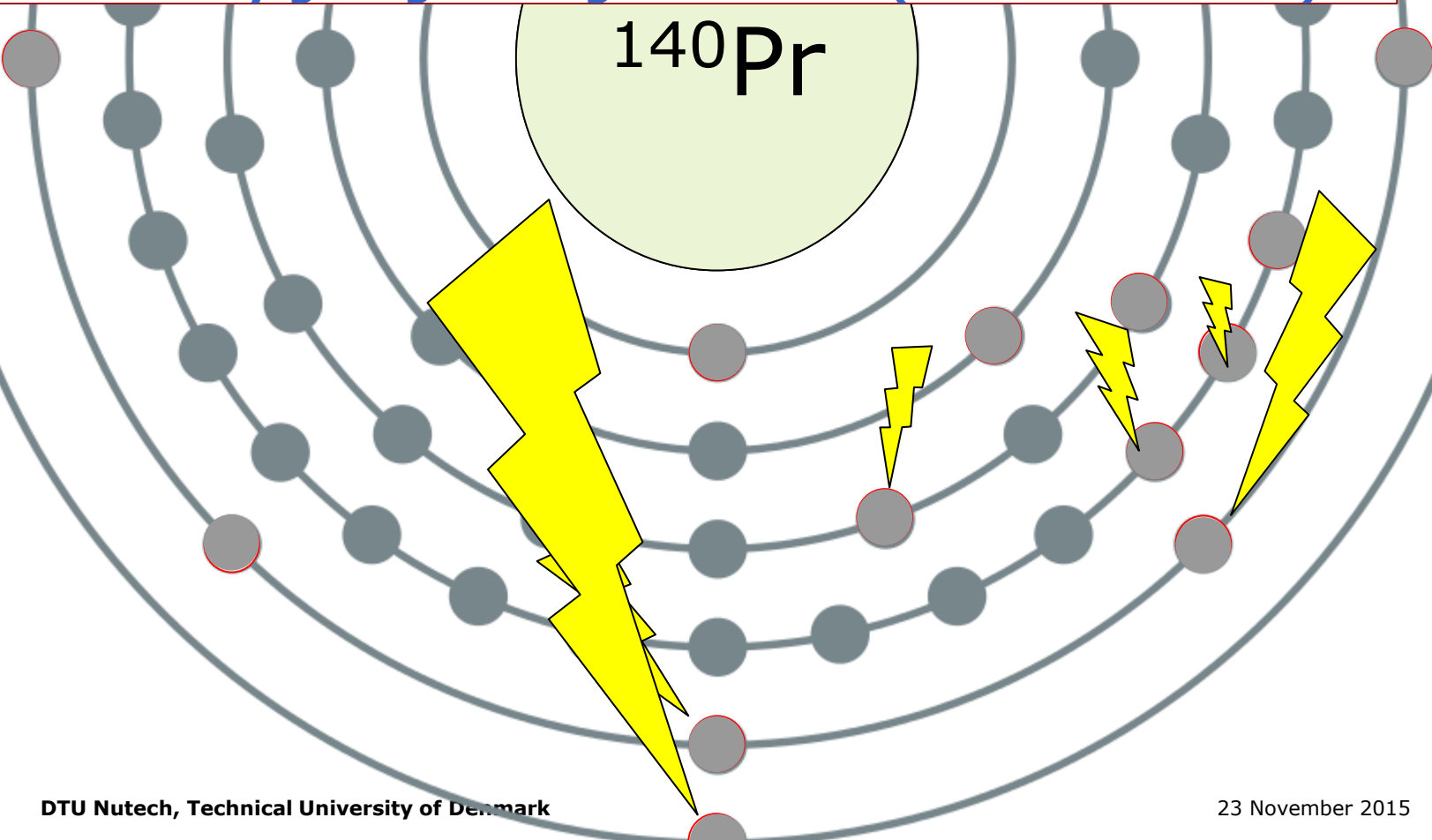
^{140}Nd EC decay creates ^{140}Pr with an atomic hole

that stabilizes by electron transitions

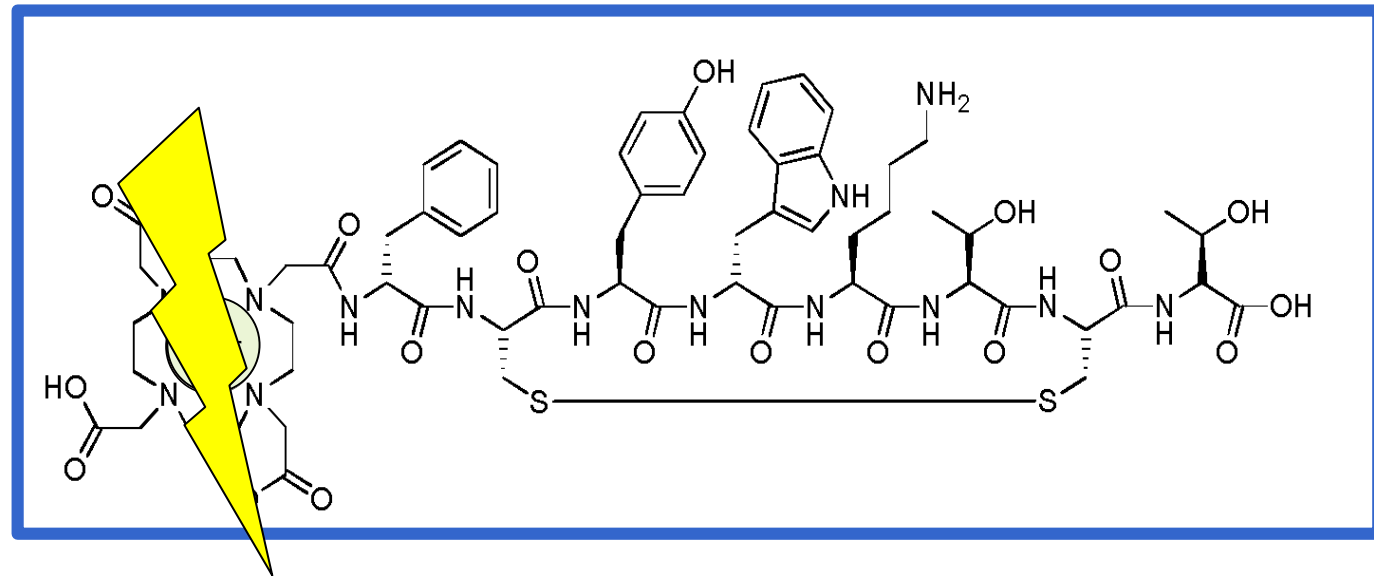
which kick off more e-'s (Augers) and make more holes

ultimately giving an Auger Cascade (e-'s:10eV-50keV)

^{140}Pr



The result of EC decay with our vector:

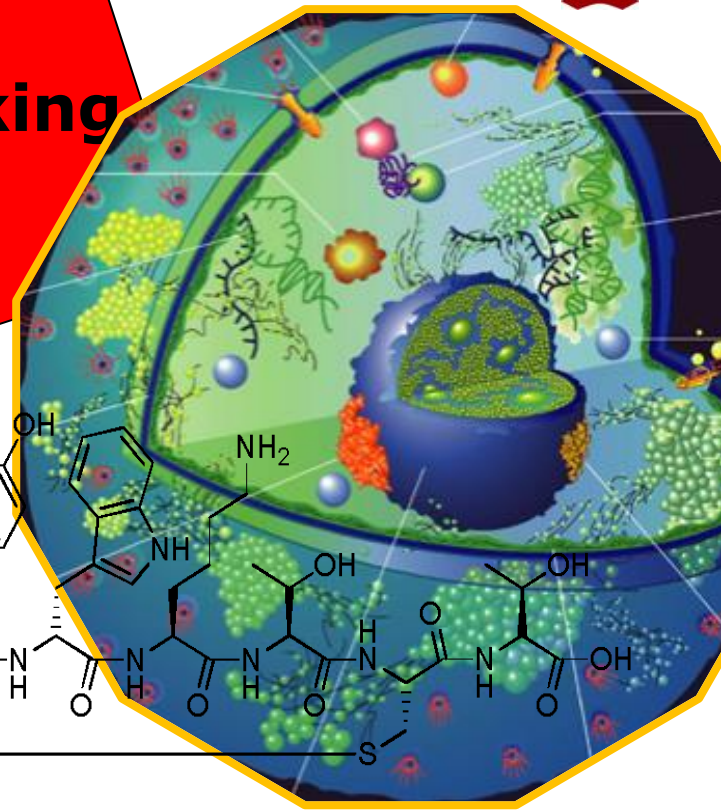
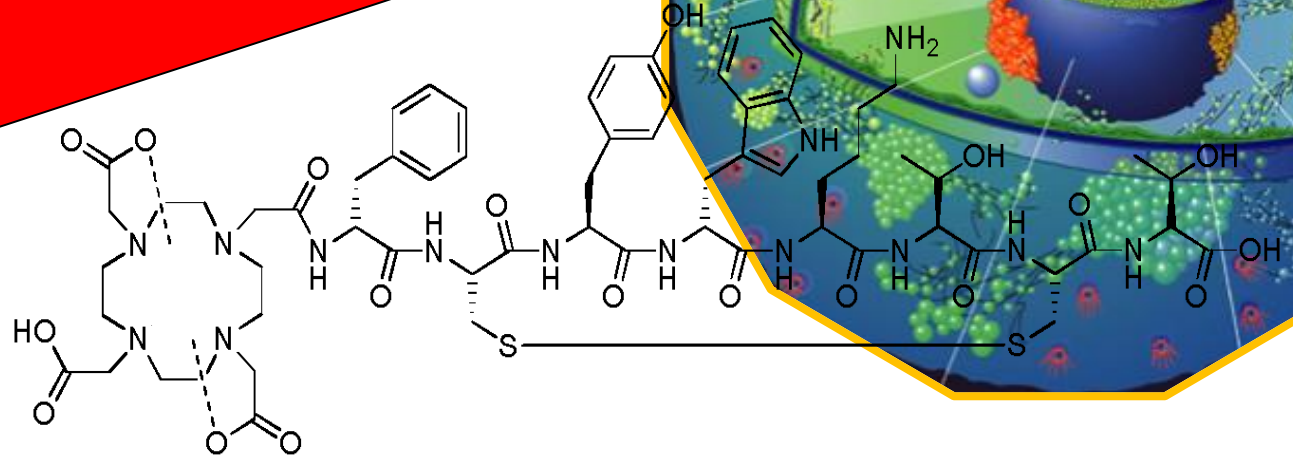


3 minute $t_{1/2}$ clock begins ticking

Blood Flow

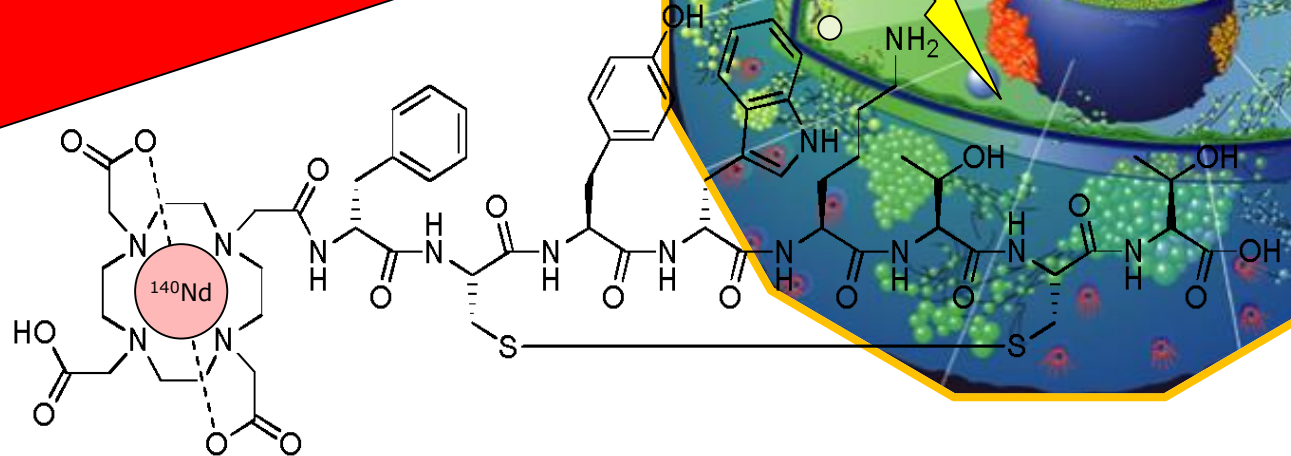
$\beta+$

^{140}Pr



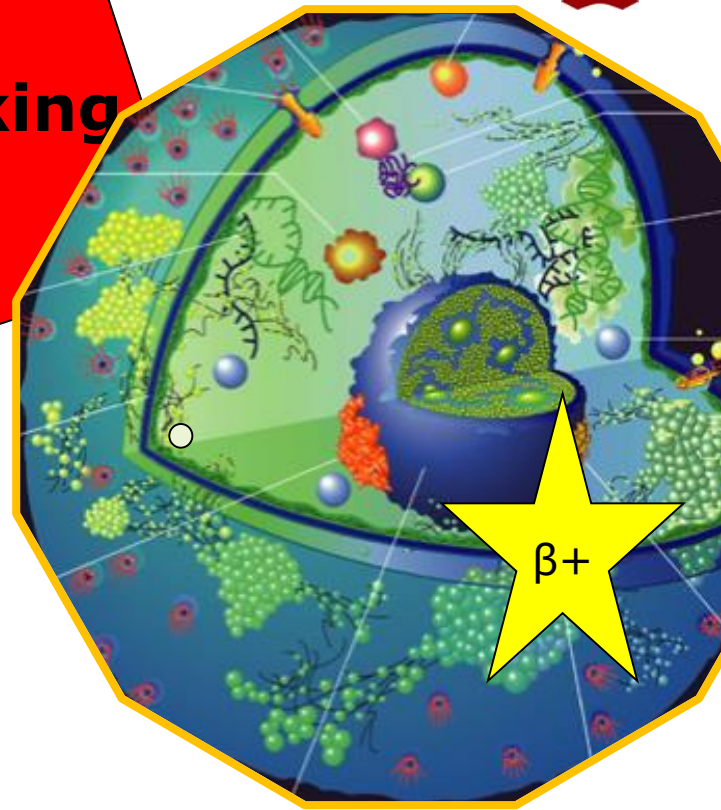
3 minute $t_{1/2}$ clock begins ticking

Blood Flow



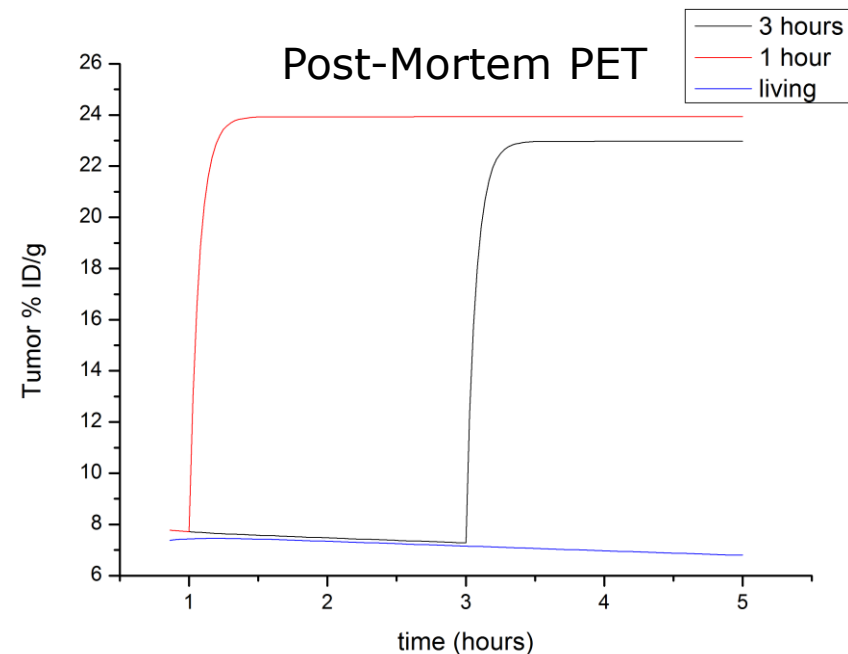
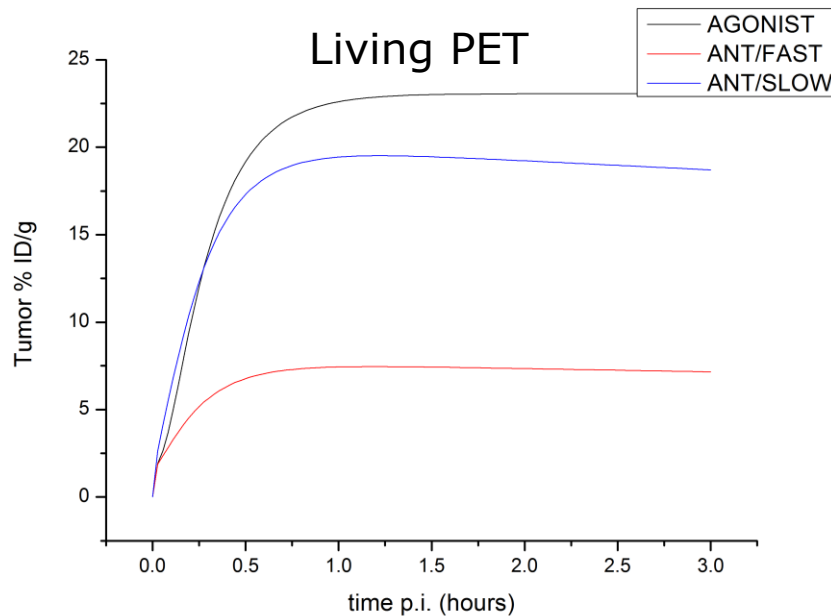
3 minute $t_{1/2}$ clock begins ticking

Blood Flow

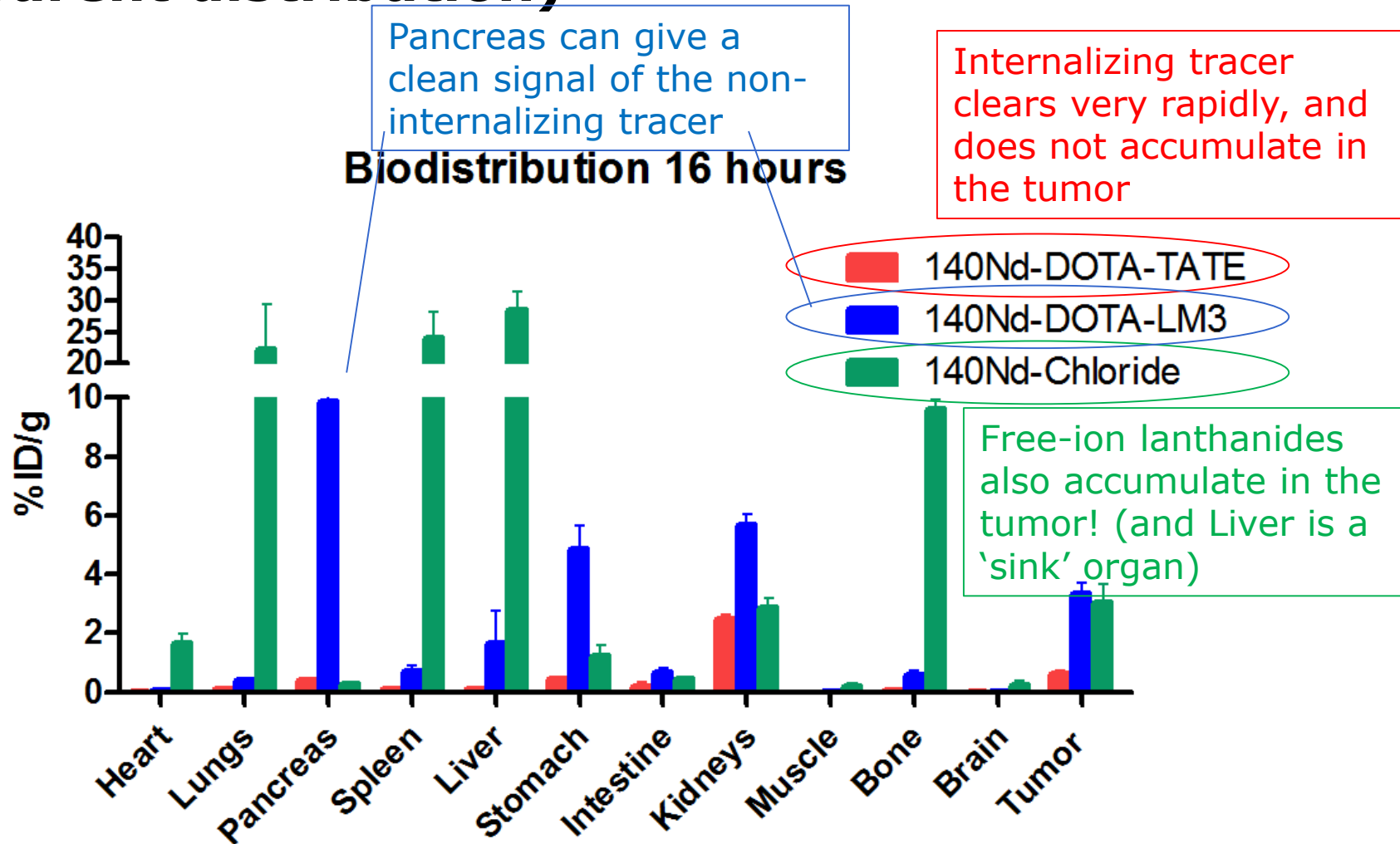


Consequences of the hypothesis

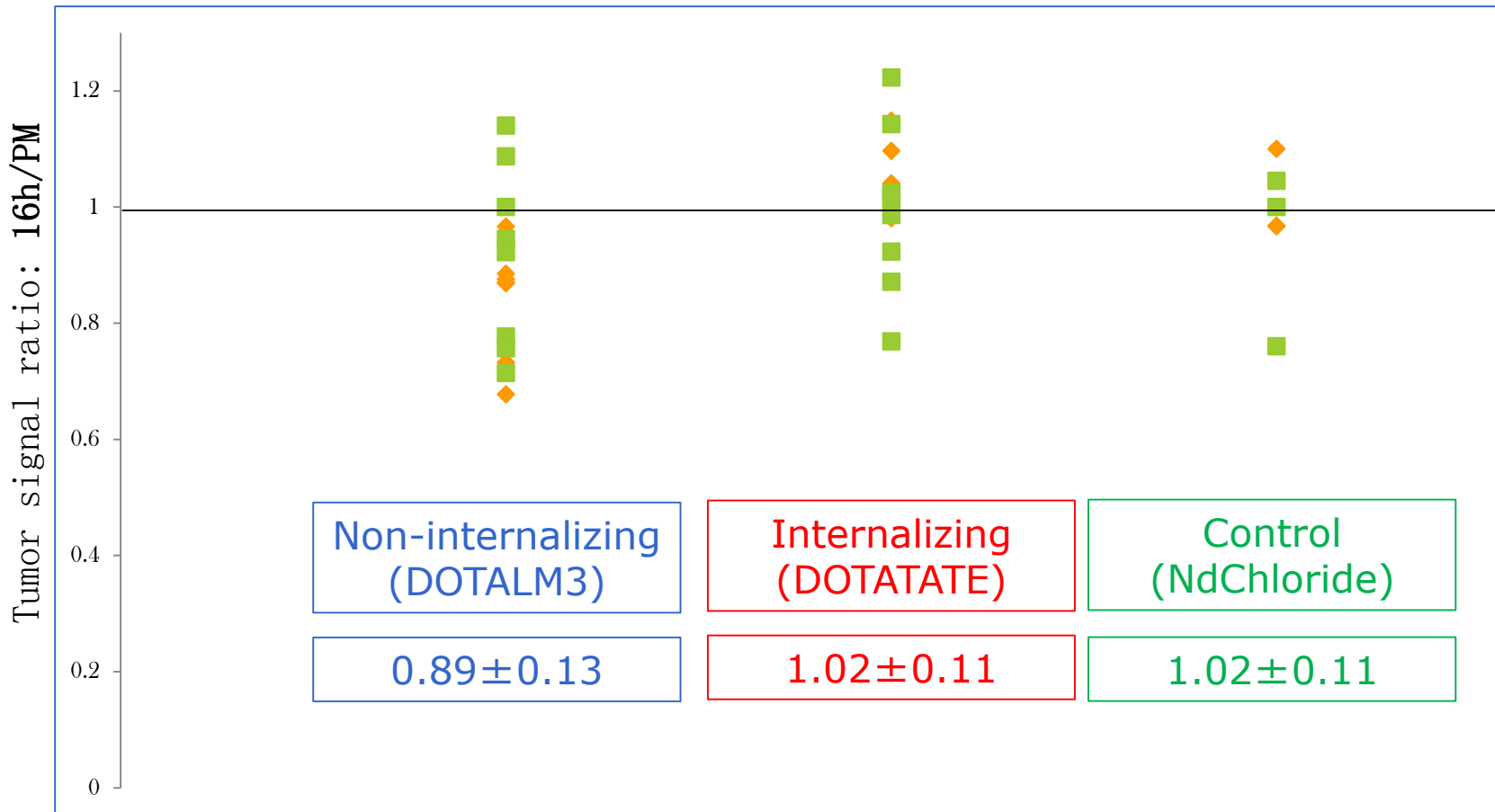
- ^{140}Nd DOTATATE (**internalizing**) will give a PET signal that is localized on tumors (or cells expressing the receptor).
- ^{140}Nd DOTALM3 (**non-internalizing**) will give a redistributed PET signal.
- Experimental procedure: Inject mice which have sst2+ tumors with each construct and compare the images when pre- and post- mortem (after 'equilibration' of the tracer distribution)



Results: Post-Mortem Biodistribution (parent distribution)



Cross your eyes: Tumor ratio (16h/PM)



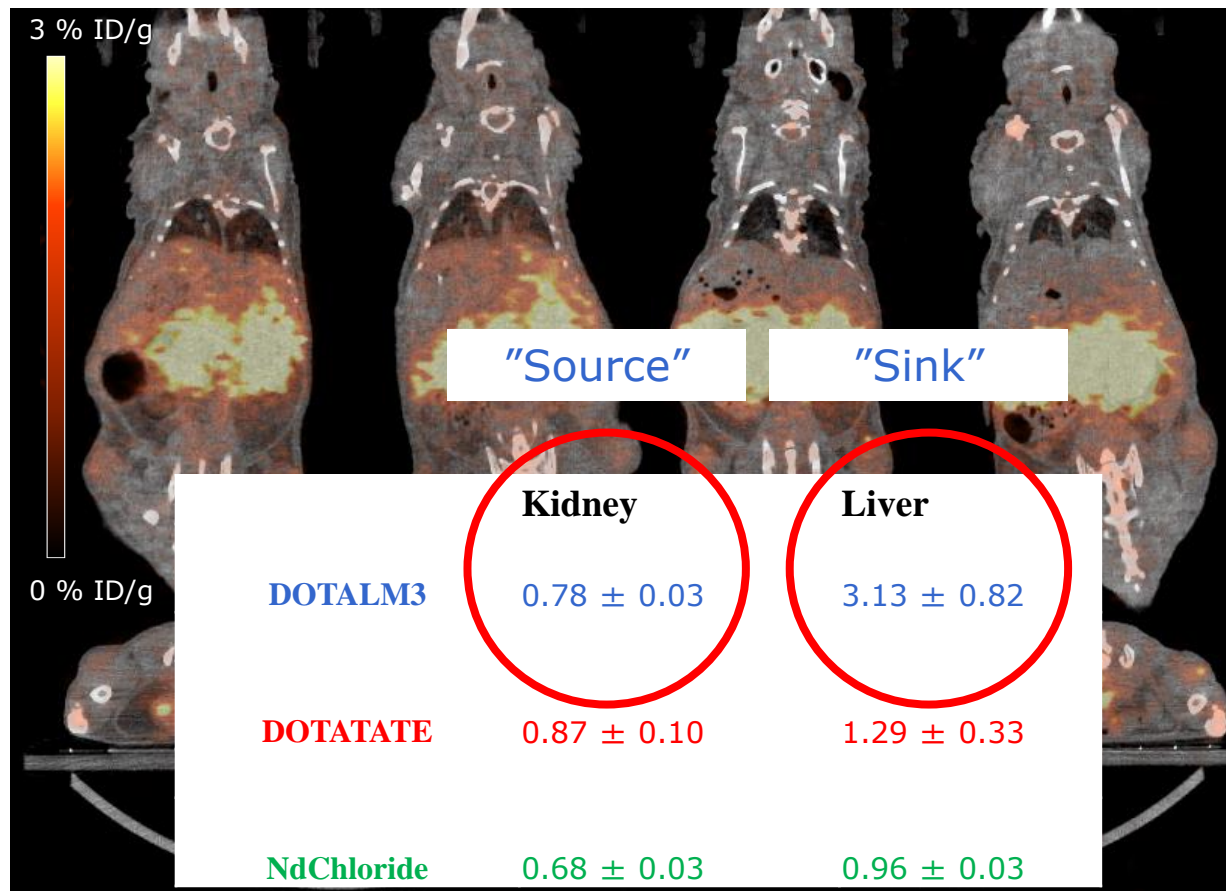
PET study: Non-Internalizing (DOTALM3)

16h = daughter distribution

Post-Mortem = parent distribution

16 hours

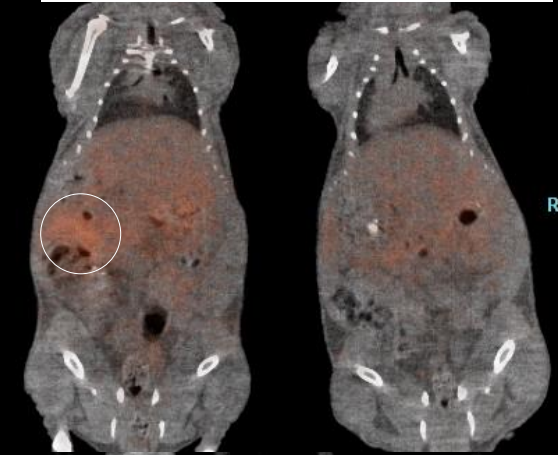
Post-Mortem



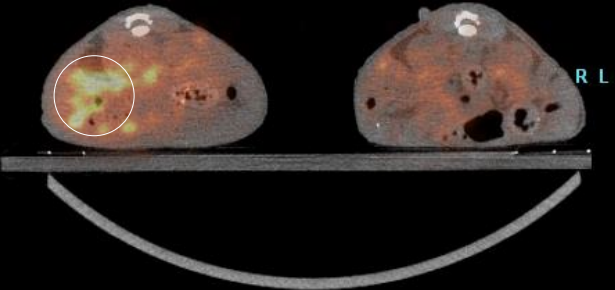
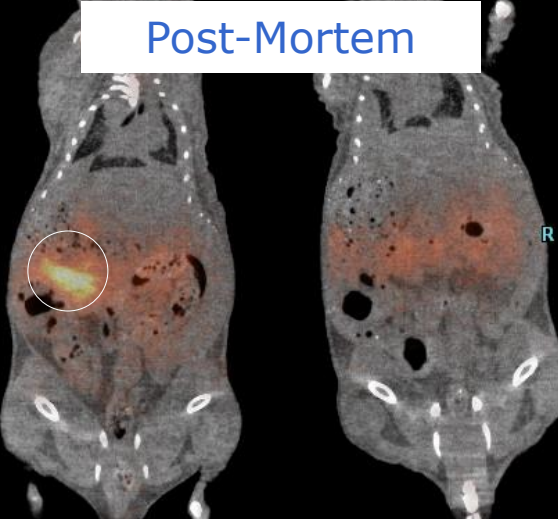
Reset the scale, and you can see the pancreas: **Non-Internalizing DOTALM3**

Ratio(16h/PM):
 0.44 ± 0.08

16 hours



Post-Mortem



Conclusions

- With careful optimization, internalization status might be determined using ^{140}Nd or ^{134}Ce PET.
- Requires high specific activity (at least in the sstr2 system)
- Determining the diffusion rates will depend upon having both ^{134}Ce and ^{140}Nd in high yield.
- Next steps: use a better perfused tumor model; introduce a 'washout' injection; triple coincidence w/ ^{44}Sc (?).

Thank you for your attention!

Thanks to the behind-the-scene contributors at ISOLDE!