Geant4 Modeling of Targeted Radionuclide Therapy for Brain Metastasis

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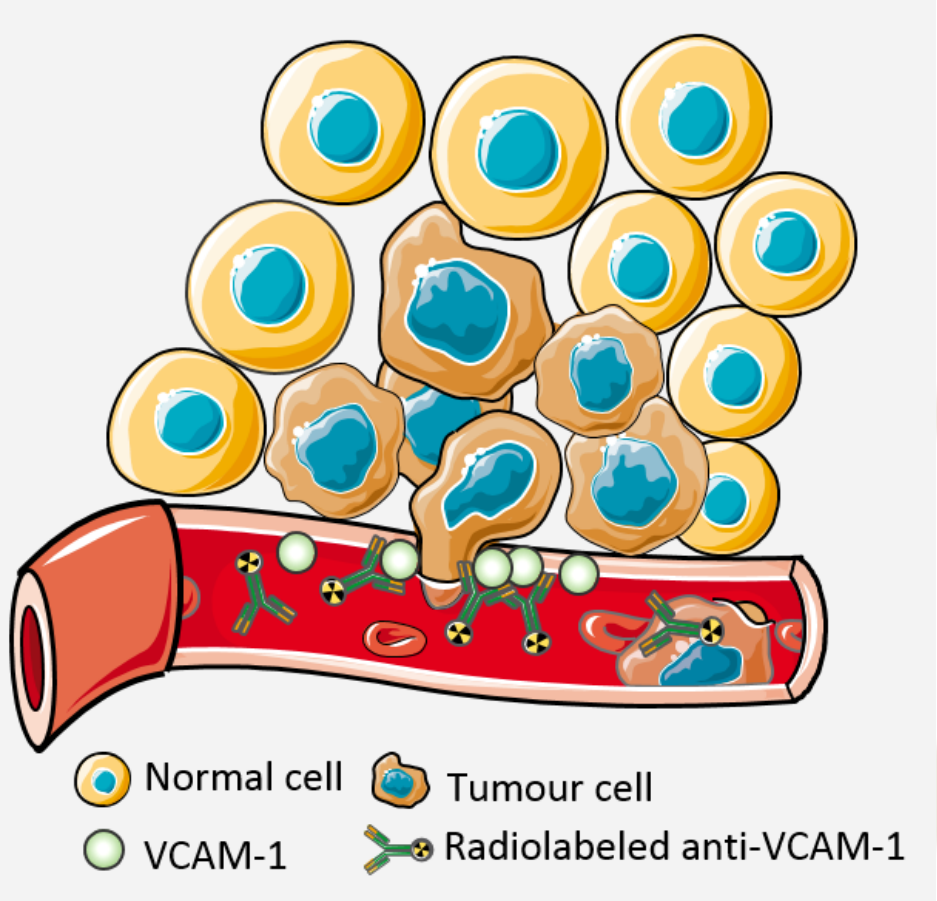
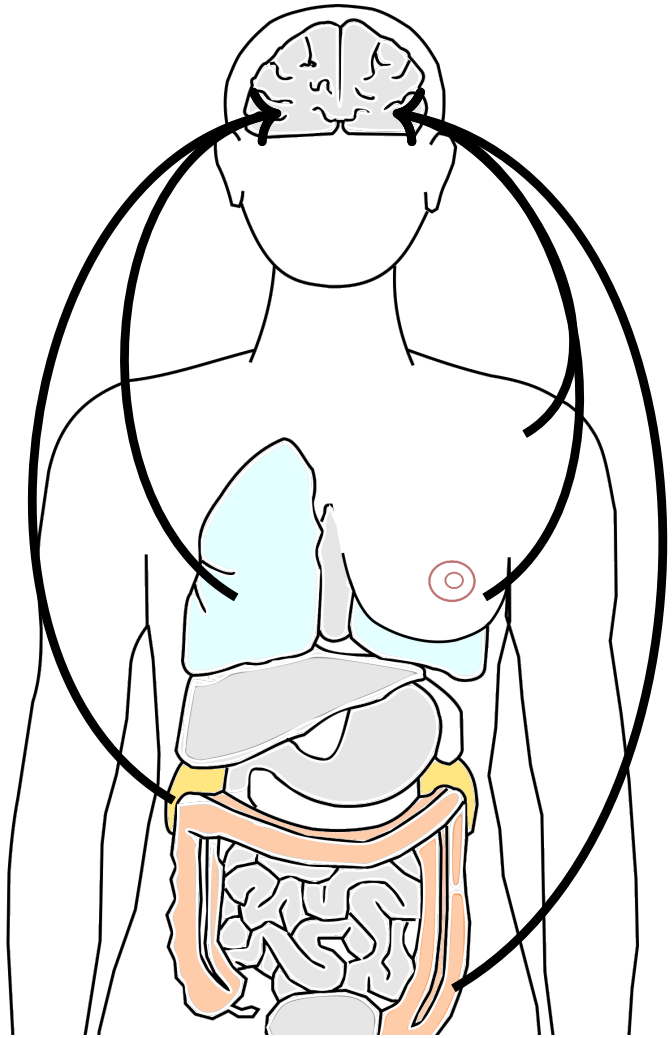
Today's Talk

1. **Biomedical Motivation**
2. **Simulation Approach**
3. **Results**



Brain Metastasis



Barnholtz-Sloan *et al*

Journal of Clinical Oncology 2014

Breast Cancer ⟶ **Brain Metastasis**

10-16% of patients

- +10% asymptomatic
- HER2+ Increased Risk($> 50\%$)

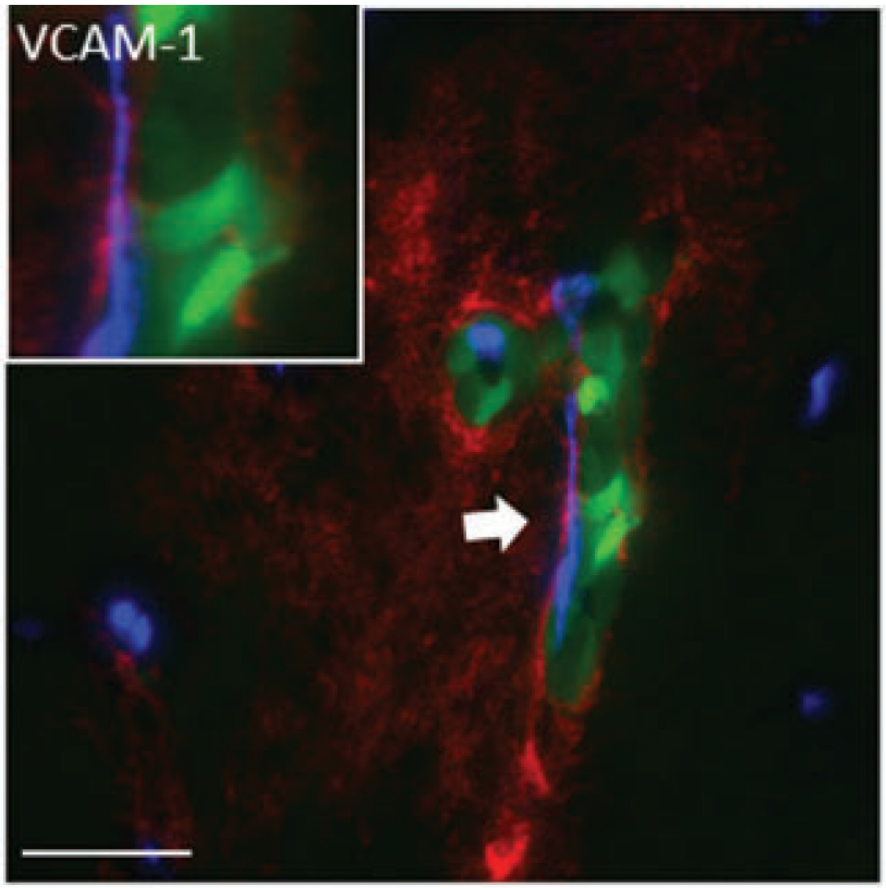
32 mos from initial diagnosis

- ER+ Longer Interval
- HER2-/ER-/PR- Shorter Interval

Leone and Leone, Exp Hematol Oncol 2015

VCAM-1

(Vasculature Cell Adhesion Molecule-1)



Green: Tumor Cells (4T1-GFP)

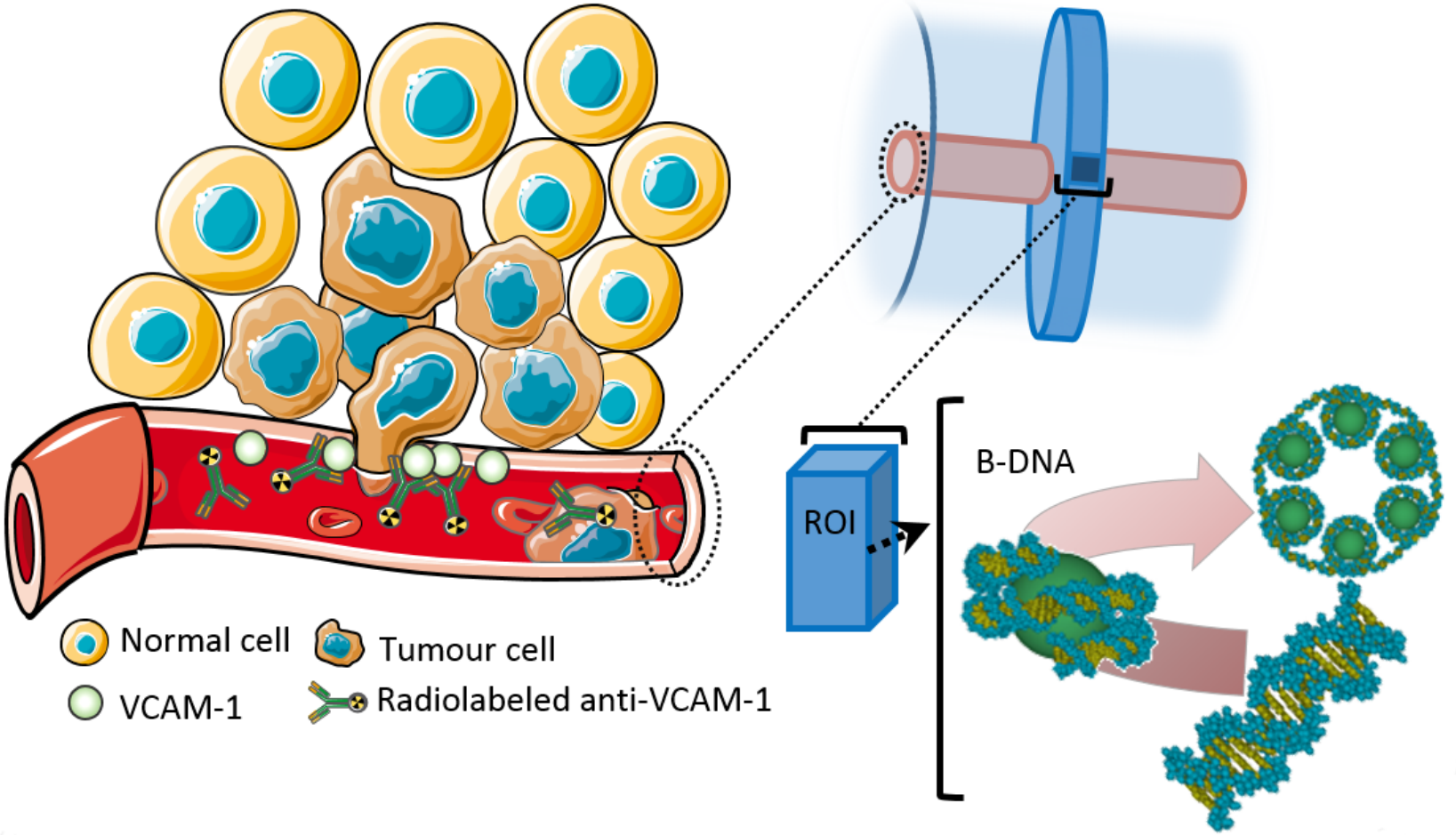
Red: VCAM-1

Blue: Endothelial Cells
(von Willebrand Factor)

Scale: 50 μm

Soto *et al* Neuro-Oncology 2014

Simulation Approach

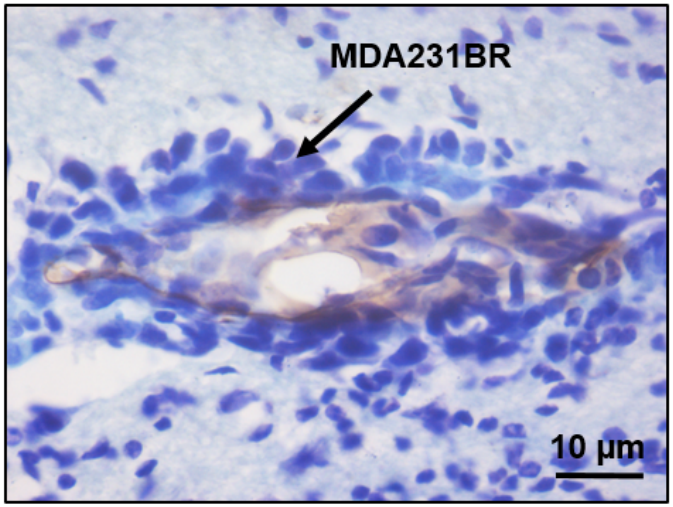


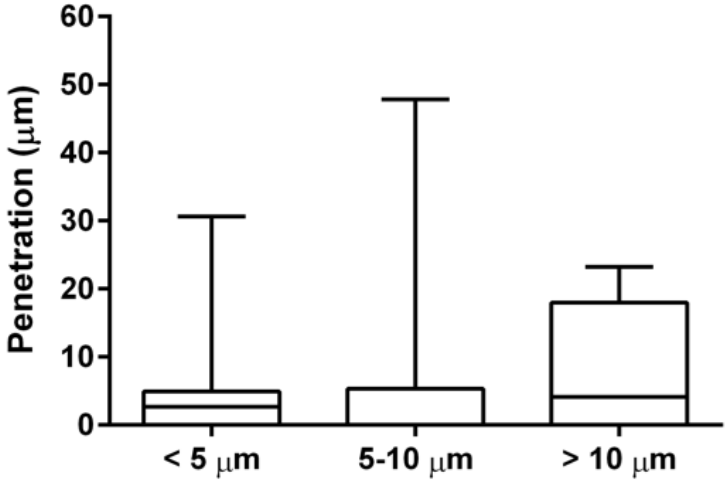
Falzone *et al*, Theranostics 2017 (In Press)

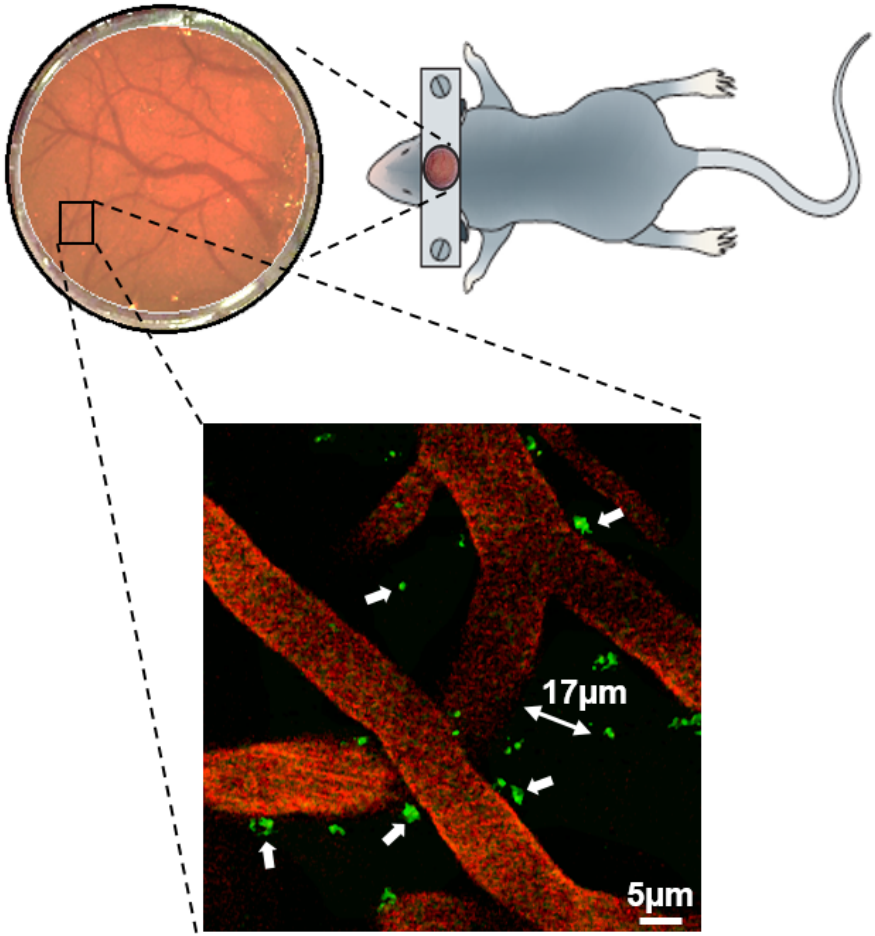
Research Questions

- Does vessel diameter and length of VCAM binding region significantly change dose profile?
- Which isotopes deliver dose to the targeted depths with minimal dose to healthy tissue?
- How does RBE vary over the treatment depth and differ between isotopes?
- How important is retention of daughter nucleus at binding site?

Mouse Model

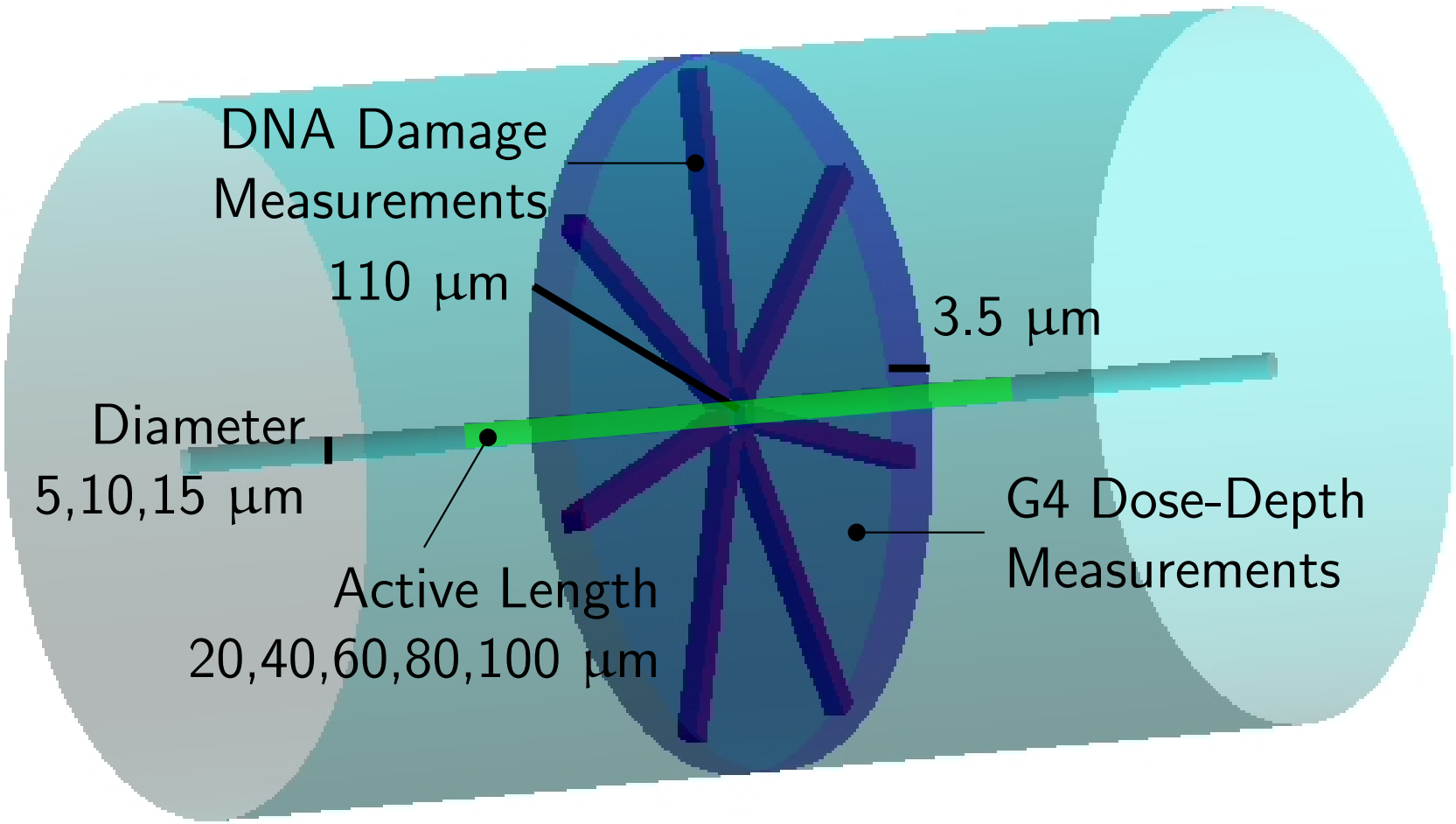






Falzone *et al*, Theranostics 2017 (In Press)

Geant4 Geometry

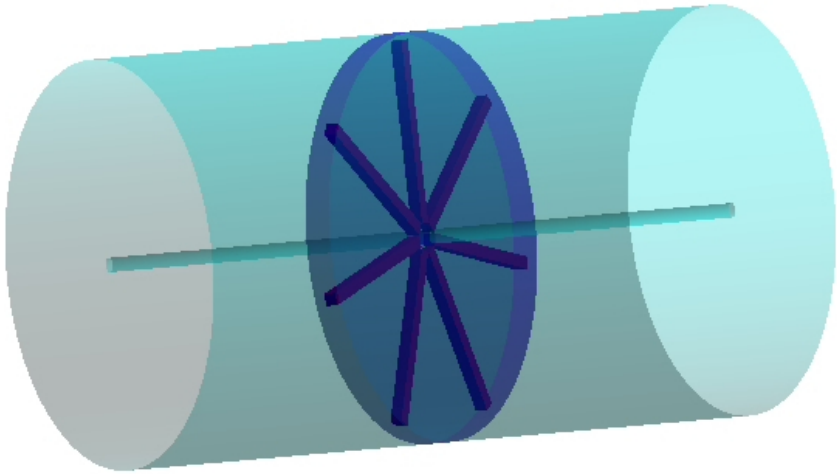


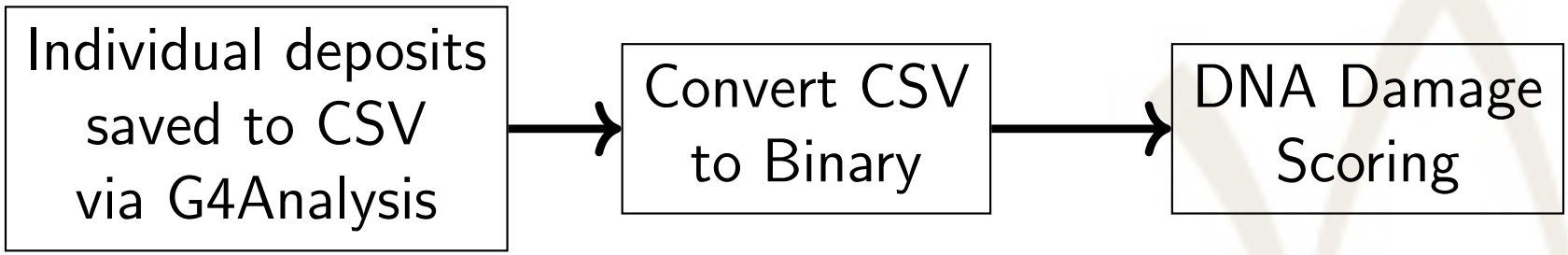
Geant4 Simulation Parameters

- Version 4.10.02.p02 in multithreaded mode
- Entire decay chain of isotope
  - α: ^{225}Ac, ^{213}Bi, ^{212}Pb, ^{211}At, ^{149}Tb
  - β: ^{177}Lu, ^{161}Tb, ^{90}Y
  - Auger electron: ^{124}I, ^{111}In, ^{89}Zr,^{67}Ga
- Liquid water, $\rho = 1.06$ g/cm^3
- Livermore physics models used (primarily)
- Electrons deposited locally if $E < 8.0$eV
- G4Analysis records CSV files of individual interactions in specific volumes

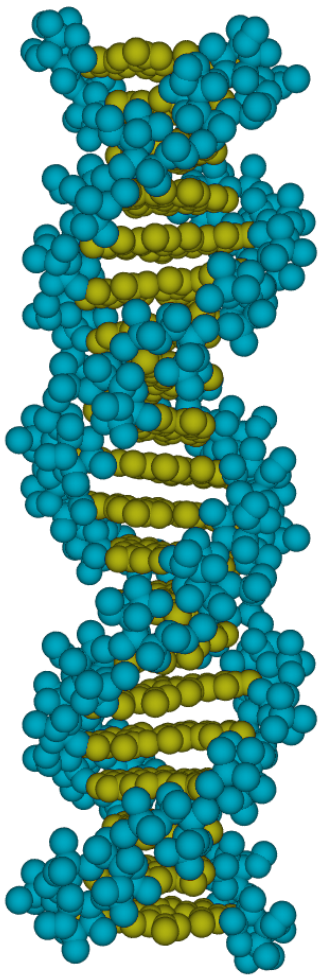
For DNA Damage Analysis

- G4DNA models enabled for low energy particles
- Detector comprised of radial bars
- Buffer region of 3µm outside detector

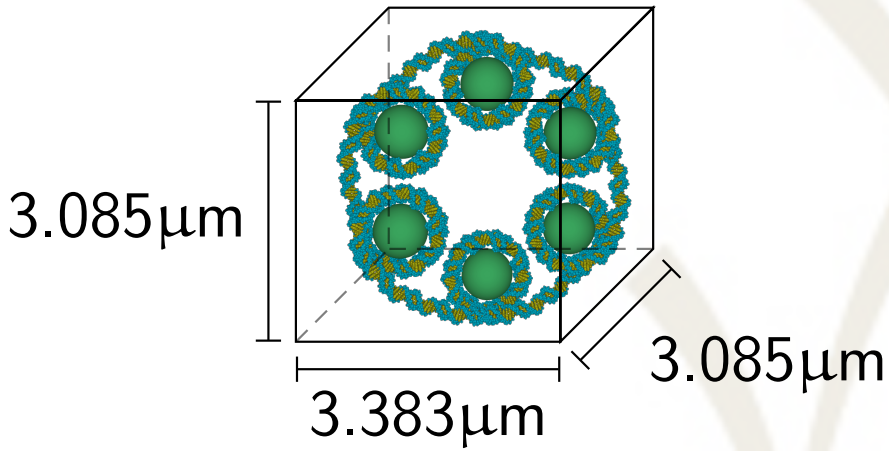




B-DNA Model

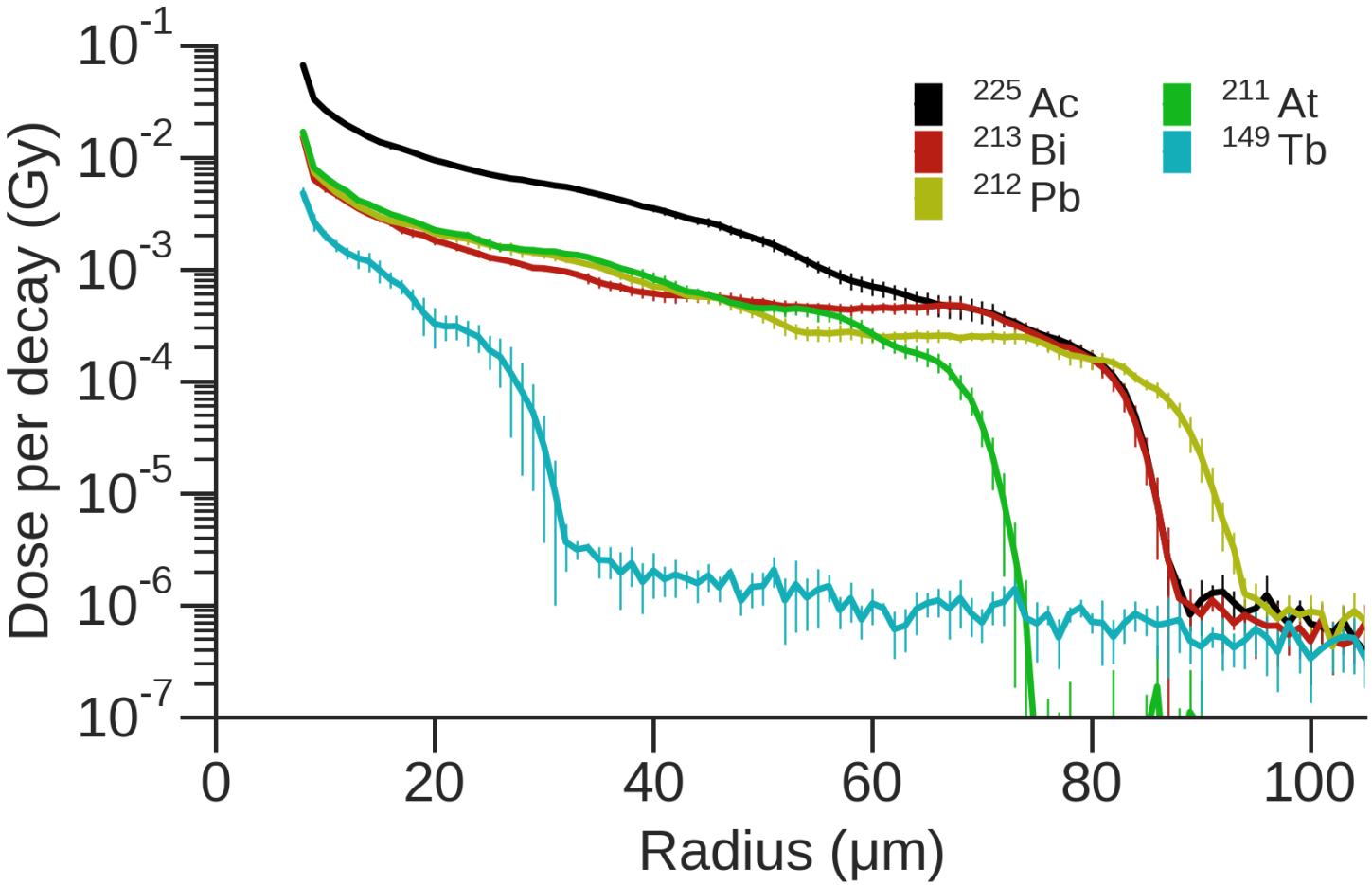


- SSB for $\geq$ 8.0 eV in sugar-phosphate group
- DSB if two SSB within 10 bp
- Only direct damage
- ^{60}Co used for RBE
  (DSB yield of 3.60 $\pm$ 0.05 per GbpGy)



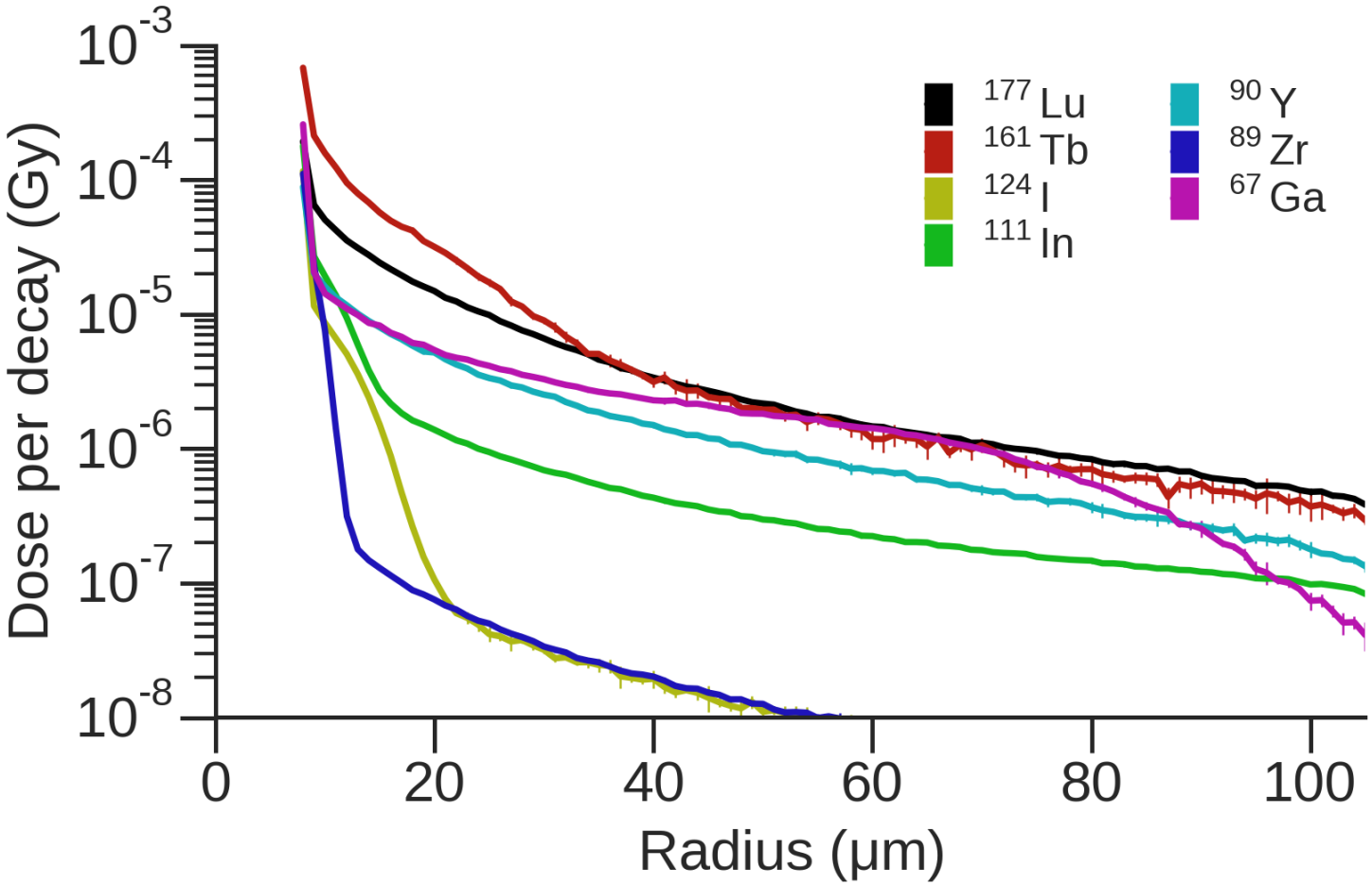
Bernal *et al* Comp Phys Comm. 2013

Alpha Emitter Dose Profiles



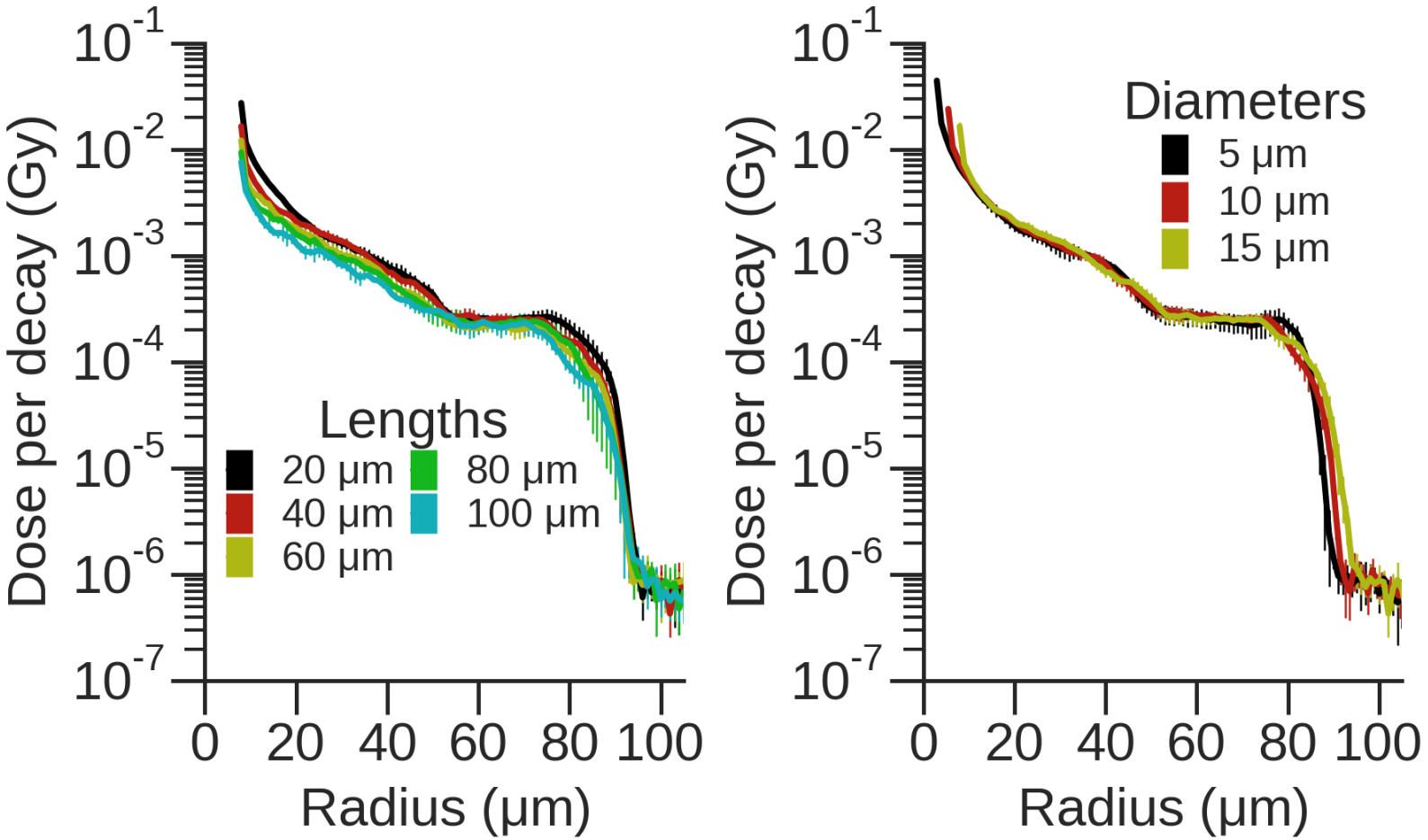
Falzone *et al*, Theranostics 2017 (In Press)

Electron emitter dose profiles



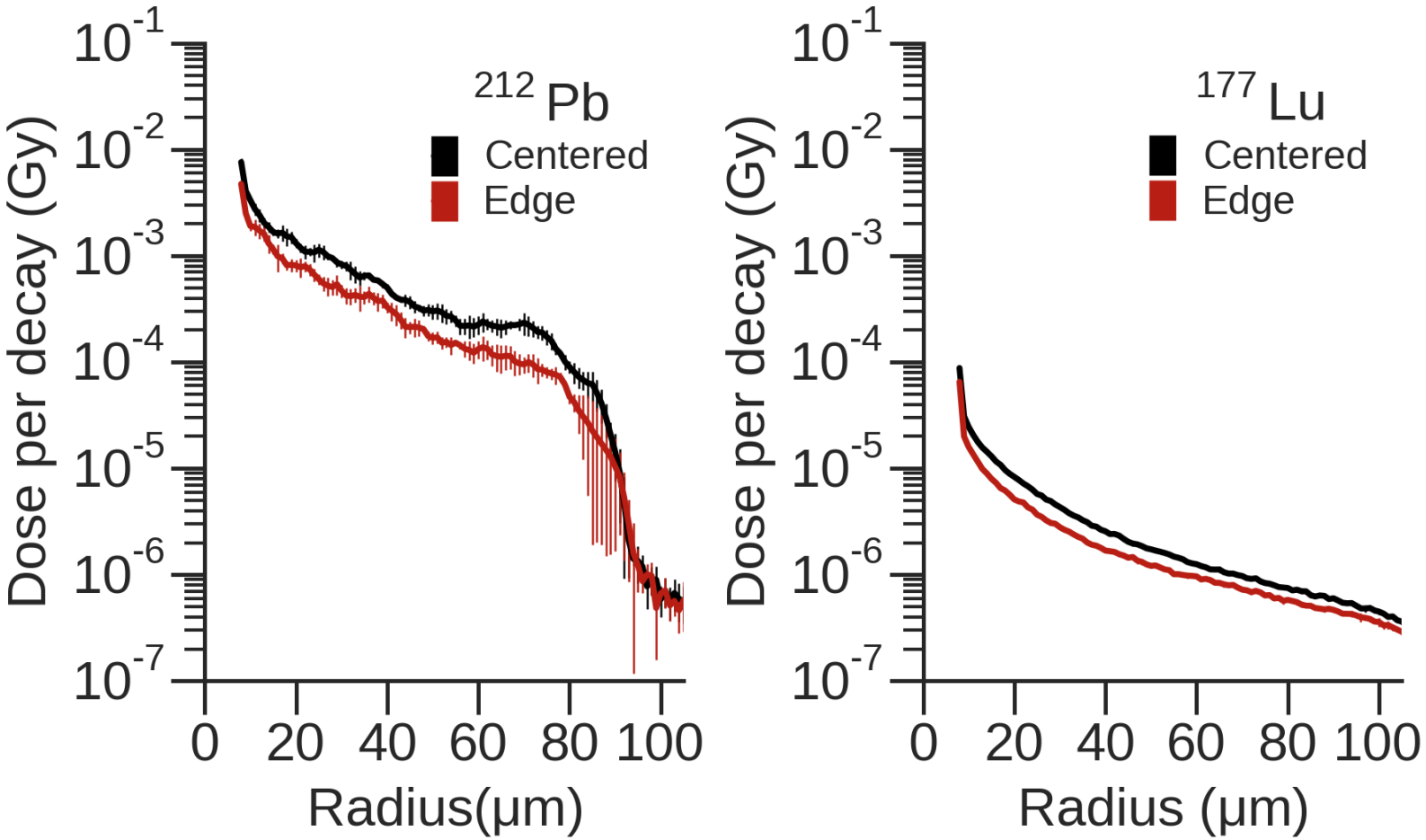
Falzone *et al*, Theranostics 2017 (In Press)

Geometry Sensitivity: ^{212}Pb



Falzone *et al*, Theranostics 2017 (In Press)

Along the Vessel



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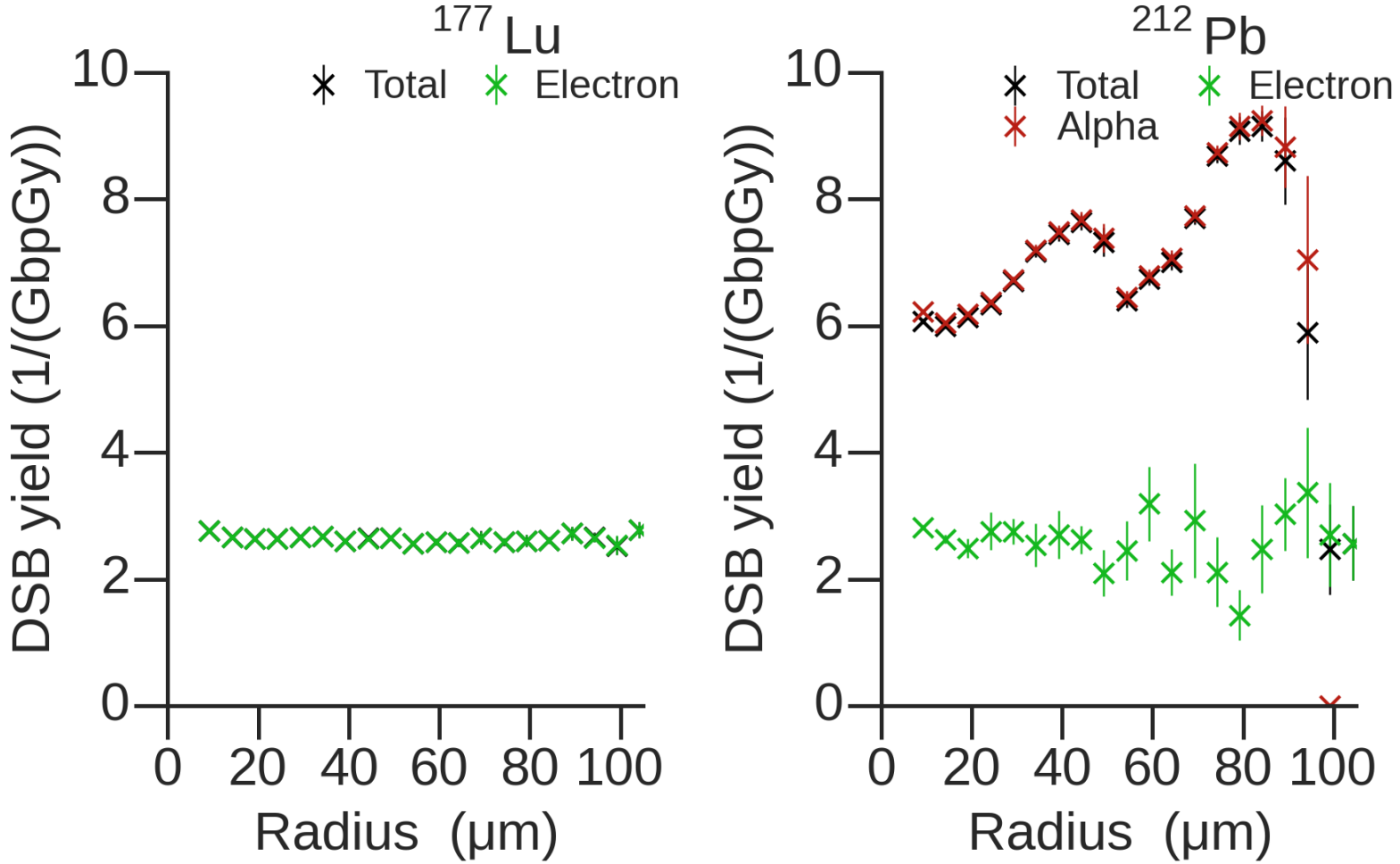
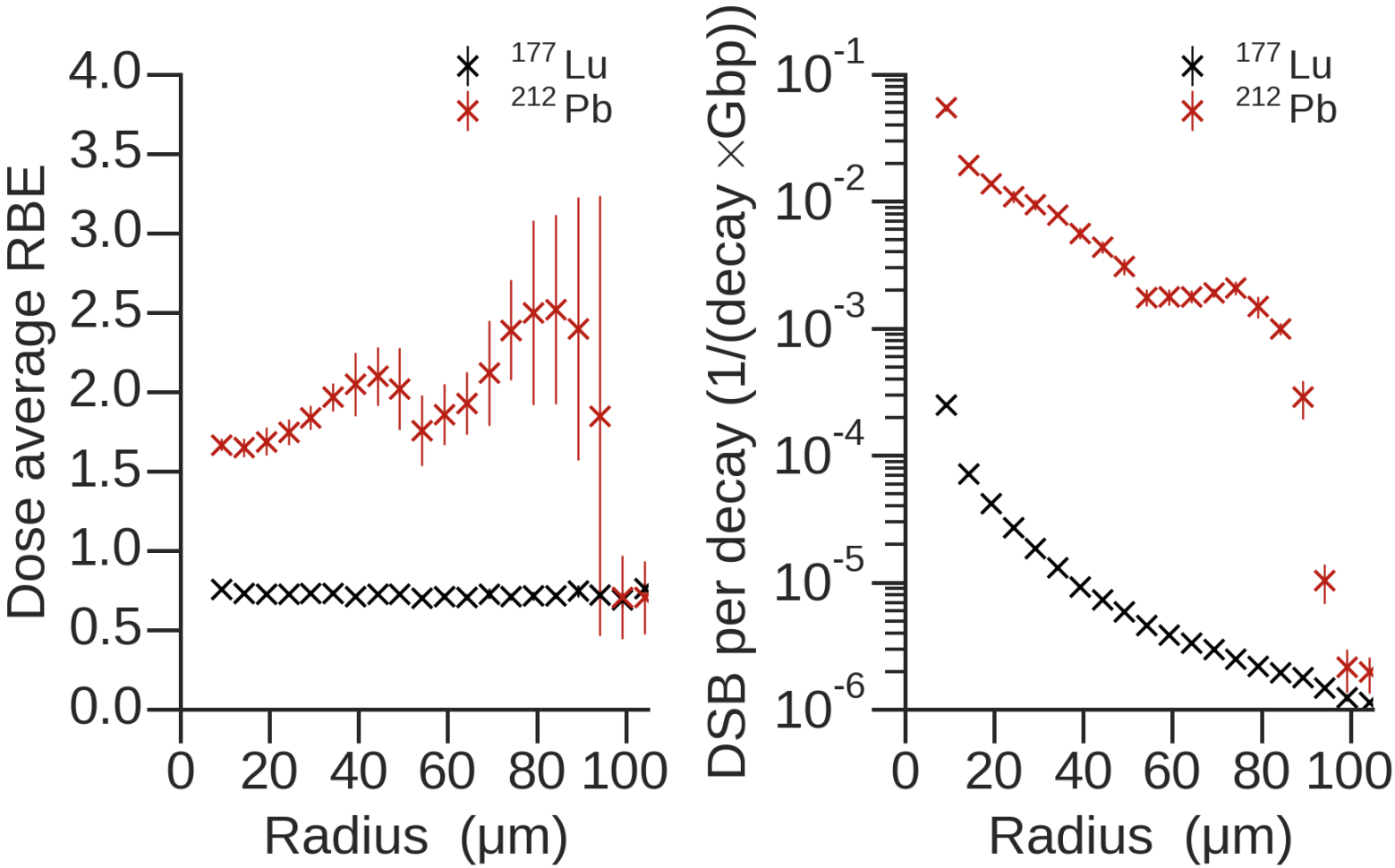
DSB Yield



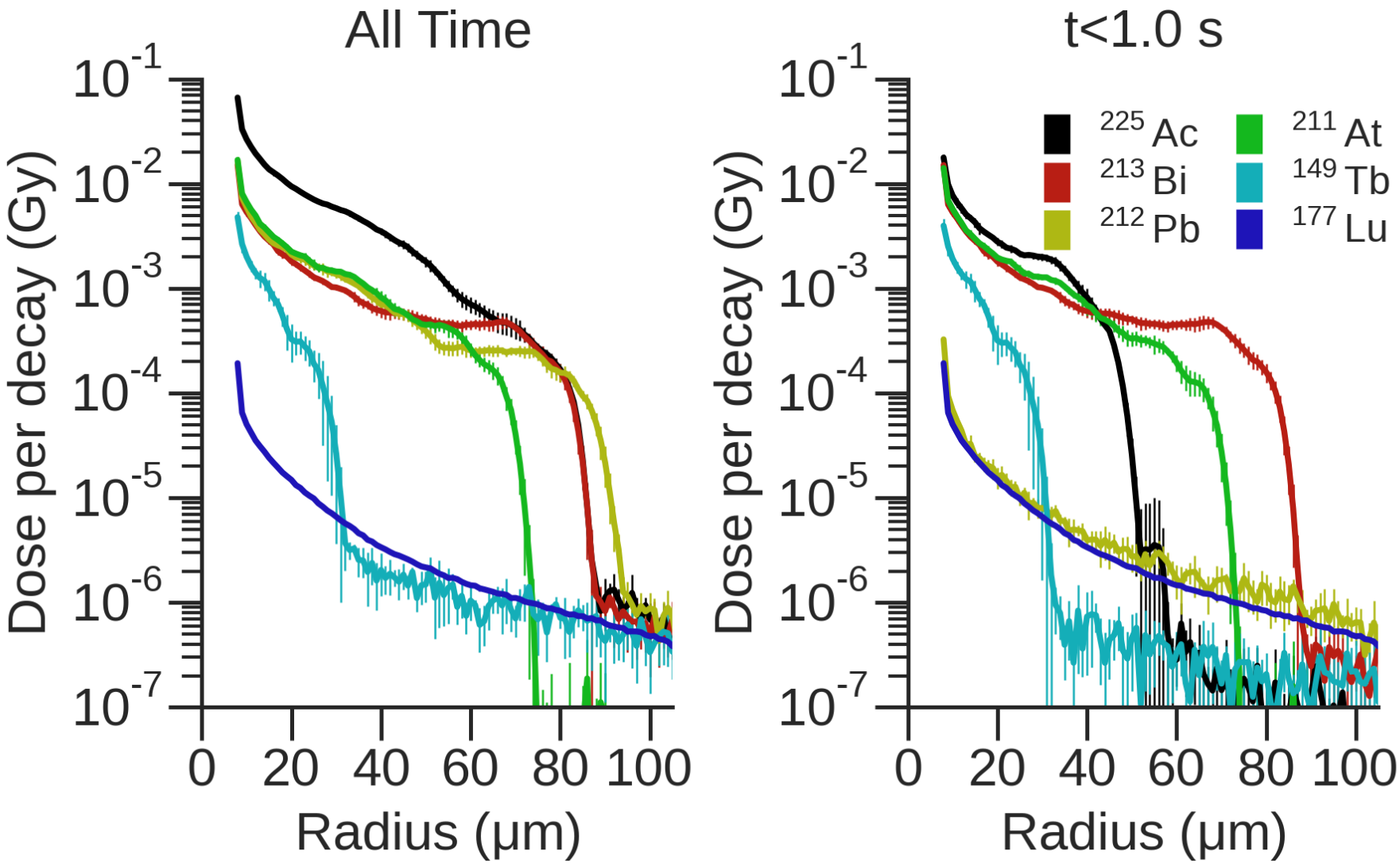
Falzone *et al*, Theranostics 2017 (In Press)

RBE

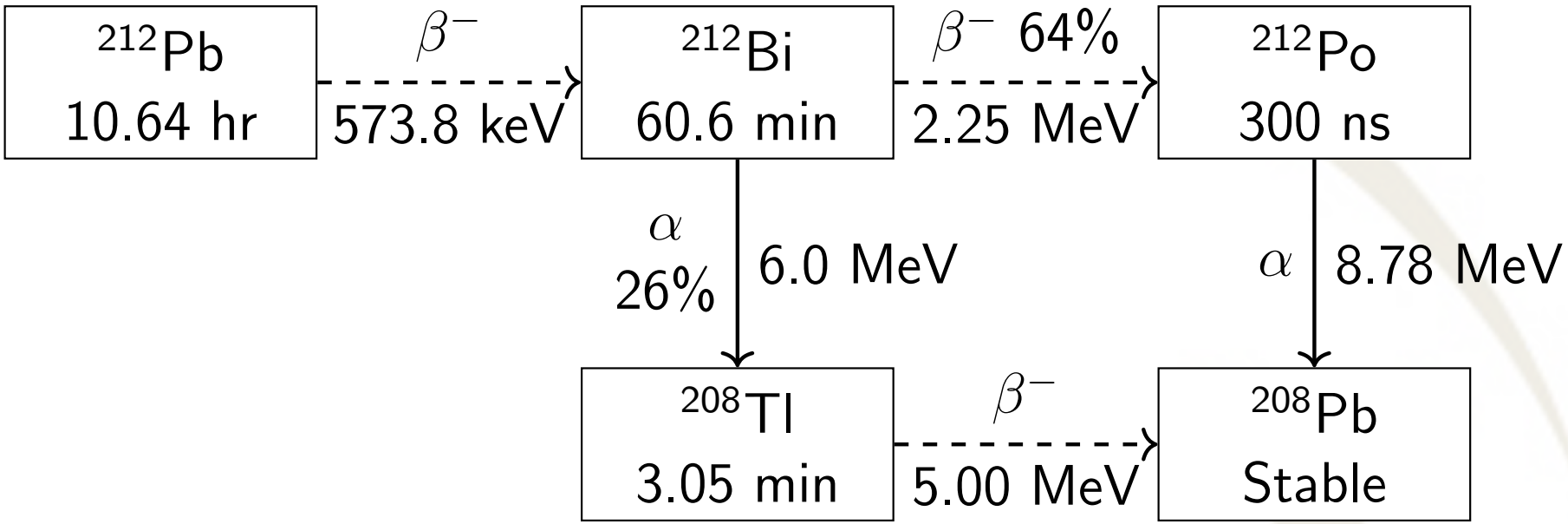


Falzone *et al*, Theranostics 2017 (In Press)

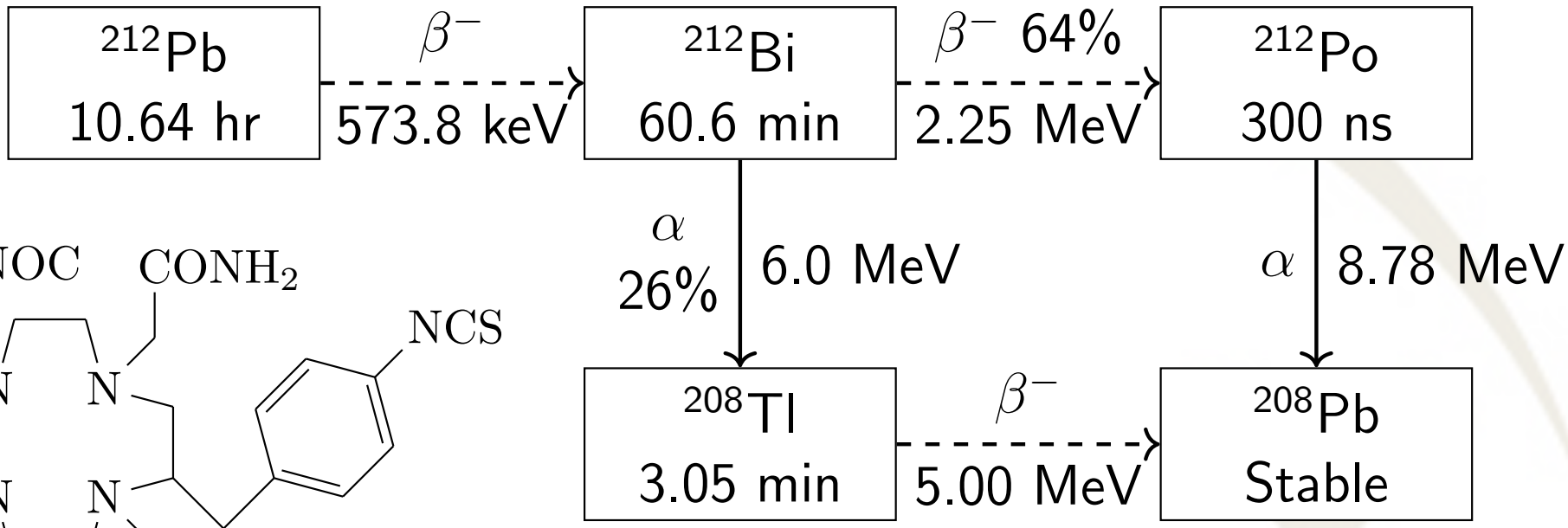
Retaining Daughters

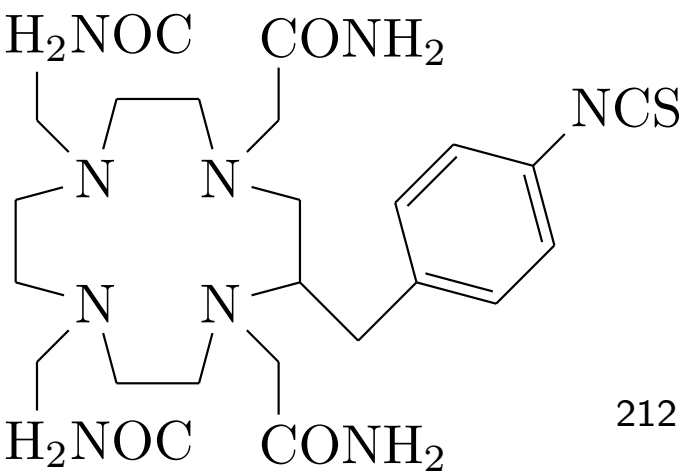


Chelation of ^{212}Pb



Chelation of ^{212}Pb





TCMC

^{212}Pb-TCMC-Trastuzumab:

Meredith *et al* Am J Clin Oncol 2016

Meredith *et al* Cancer Biotherapy and Radiopharmaceuticals 2014

Summary of Results

- Our simulation results are not very sensitive to changes in geometry.
- Alpha-emitters have a sharp decrease in dose a few cell radii from vessel.
- DSB yield per decay 600 - 800 times higher for ^{212}Pb than ^{177}Lu for relevant distances.
- The efficacy of some of the radioisotopes (^{225}Ac, ^{212}Pb) depend strongly on retention time.

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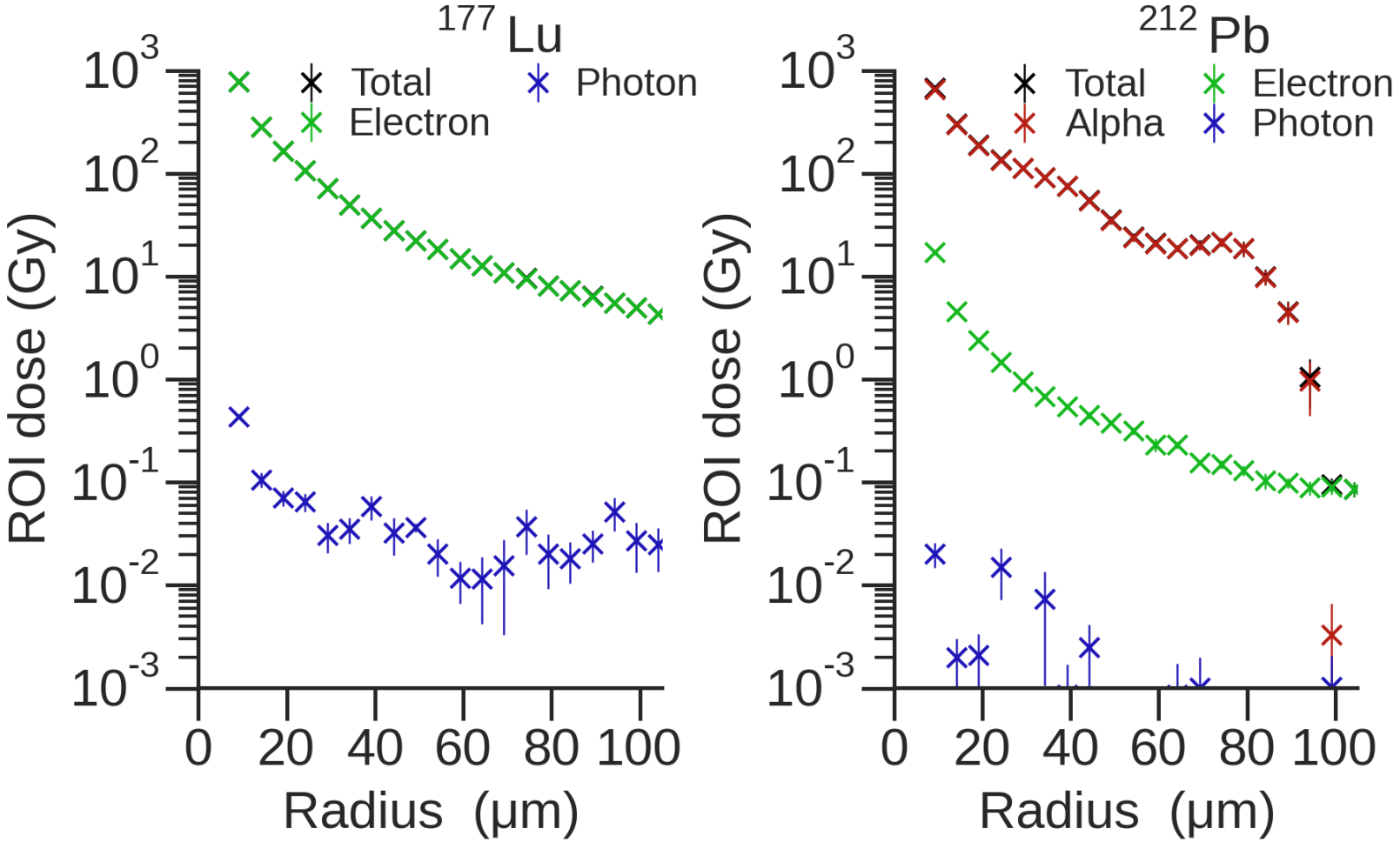
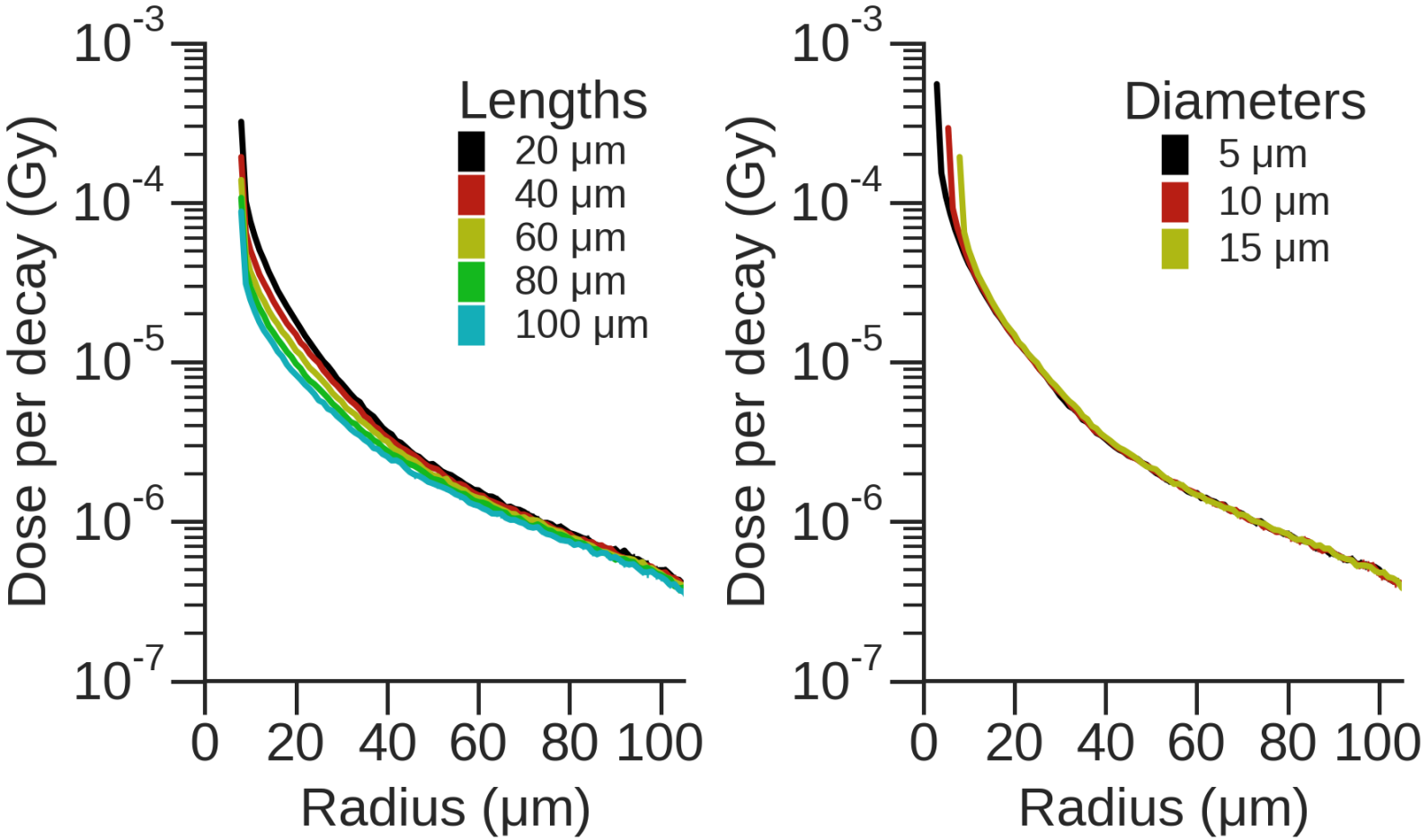
ROI Dose



Falzone *et al*, Theranostics 2017 (In Press)

Geometry Sensitivity: ^{177}Lu



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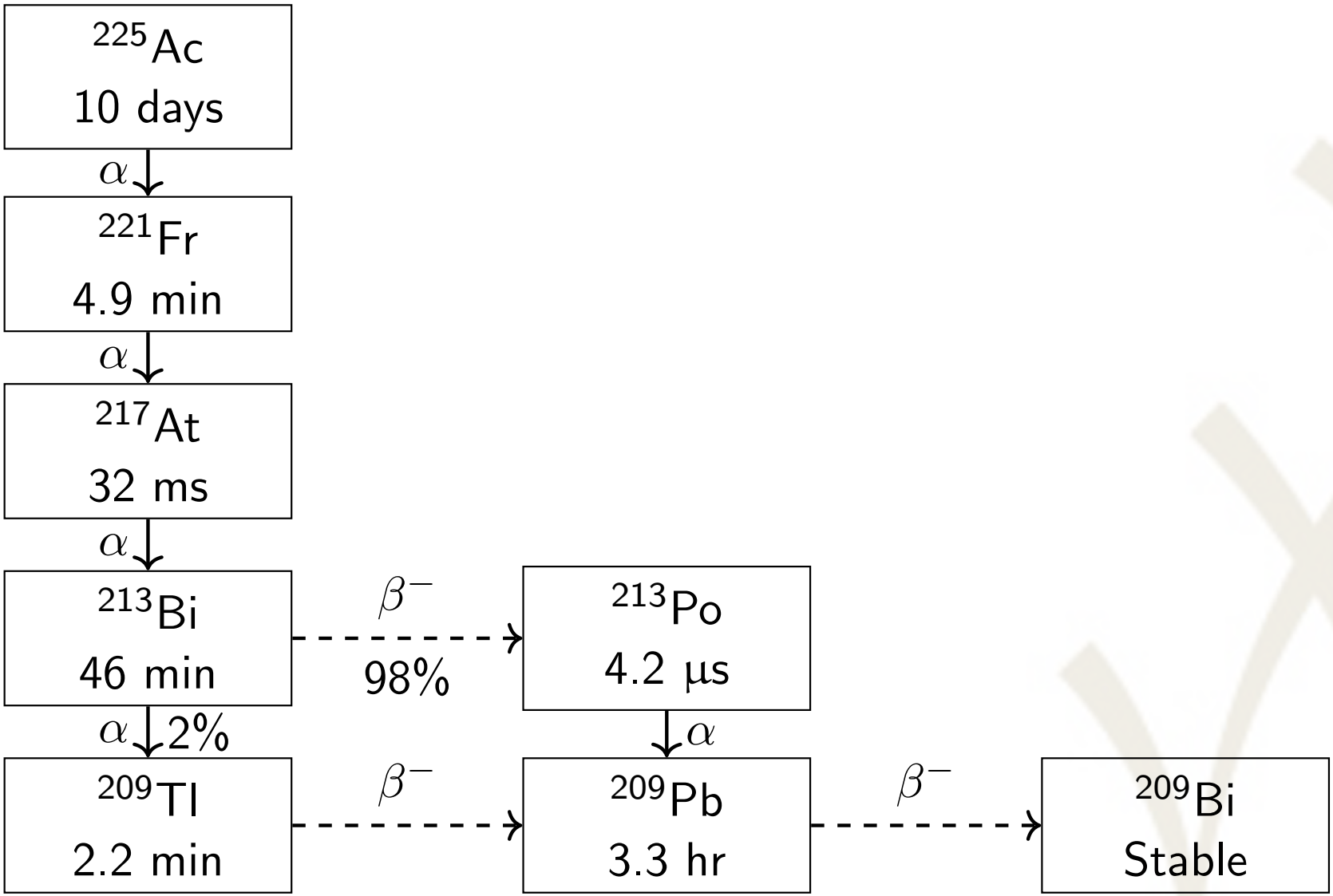
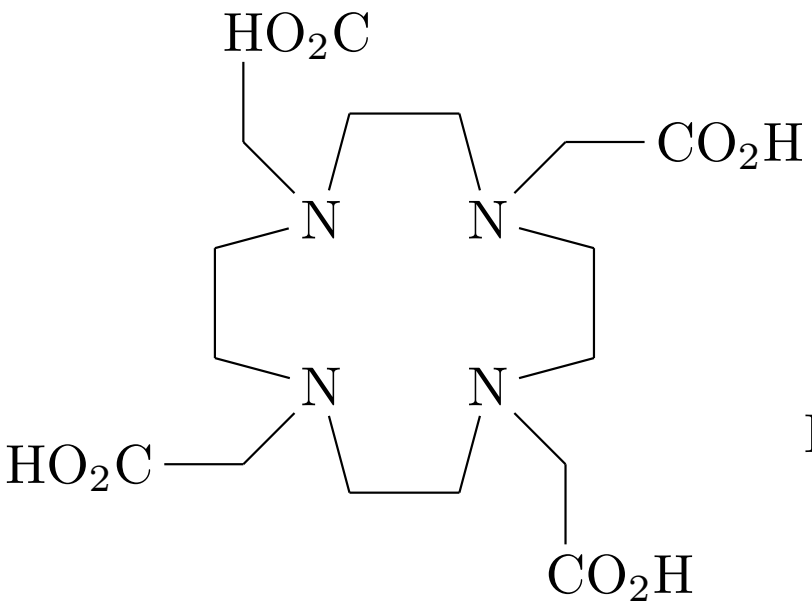
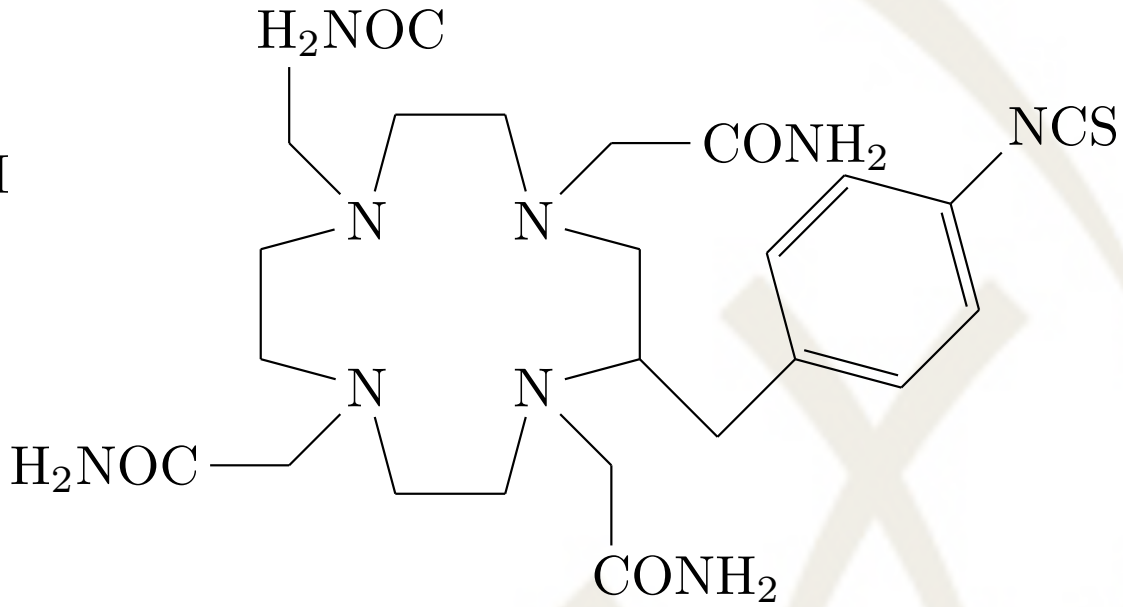
^{225}Ac Decay Chain



Chelators



DOTA



TCMC

Physics List Models

Non-DNA damage scoring regions

$e-$	MultipleScattering
	LivermoreIonisation
	LivermoreBremsstrahlung
γ	LivermoreRayleigh
	LivermorePhotoElectric
	LivermoreCompton
	LivermoreGammaConversion
proton	hMultipleScattering
	hIonisation
	DNAChargeDecrease
alpha	hMultipleScattering
	DNAChargeDecrease

alpha+	DNAExcitation
	DNAIonisation
	DNAChargeDecrease
	DNAChargeIncrease
helium	DNAExcitation
	DNAIonisation
	DNAChargeIncrease
hydrogen	DNAIonisation
	DNAExcitation
	DNAChargeIncrease

Based on microdosimetry example

DNA Damage Models

e-	ChampionElastic
	BornIonisation
	BornExcitation
	MeltonAttachment
	SancheExcitation
proton	RuddIonisation ($0 < E < 0.5$MeV)
	BornIonisation ($0.5 < E < 10$MeV)
	MillerGreenExcitation ($10\mathrm{eV} < E < 0.5$MeV)
	BornExcitation ($0.5 < E < 10$MeV)
alpha	RuddIonisation ($0 < E < 10$MeV)
	MillerGreenExcitation ($1\mathrm{keV} < E < 10$MeV)