Alpha-Emitter-Specific Dosimetry Issues

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Disclosures

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Founder: Radiopharmaceutical Imaging and Dosimetry (RAPID), LLC

Current cancer therapies

Before the cancer has spread/metastasized

- Surgery
  - Remove the tumor
- Radiotherapy
  - Deliver radiation beams focused on the tumor

Current cancer therapies

5-year survival by stage*		
Site	localized	distant
Breast	99%	30%
Colorectal	90%	14%
Lung	56%	5%
Ovary	93%	29%
Pancreas	32%	3%
prostate	100%	30%

*SEER.Cancer.gov

Current cancer therapies

After the cancer has spread/metastasized

- Chemotherapy
  - Kill rapidly proliferating cells
- Radiopharmaceutical Therapy
  - Kill targeted cells by localized radiation delivery
- Targeted Biologic Therapy (hormonal Tx)
  - Inhibit signaling pathways that tumor cells are addicted to (*i.e.*, rely on to maintain cancer phenotype)
- Immunotherapy
  - Overcome immune tolerance to cancer

Radiopharmaceutical therapy

RPT agent	Company	Indication
^{131}I-radioiodine	Jubilant Draximage	Thyroid cancer
^{131}I-MIBG	Progenics	Adrenergic^{+} tumors
^{212}Pb-trastuzumab	OranoMed	HER2^{+} tumors
^{212}Pb-PRIT	OranoMed/Roche	Undisclosed
^{212}Pb-antisomatostatin	OranoMed/Radiomedix	Somatostatin^{+} tumors
^{212}Pb-aTEM1	OranoMed/Morphotek	TEM1^{+} tumors
^{212}Pb-aCD37	OranoMed/NordicNanovector	Leukemia
^{131}I-aCD45	Actinium Pharmaceuticals	BM xplant prep
^{225}Ac-aCD33	Actinium Pharmaceuticals	Leukemia
^{90}Y-microspheres	Varian/Sirtex	Hepatic malignancies
^{90}Y-microspheres	BTG	Hepatic malignancies

Radiopharmaceutical therapy

RPT agent	Company	Indication
Lutathera (^{177}Lu)	Novartis/AAA	Somatostatin^{+} tumors
^{177}Lu-aPSMA-R2	Novartis/AAA	Prostate, tumor neovasc.
^{177}Lu-NeoBOMB1	Novartis/AAA	Bombesin^{+} tumors
Xofigo (^{223}Ra)	Bayer	Bone mets
HER2-TTC (^{227}Th)	Bayer	HER2^{+} tumors
PSMA-TTC (^{227}Th)	Bayer	Prostate, tumor neovasc.
FGFR2-TTC (^{227}Th)	Bayer	FGFR2^{+} tumors
MSLN-TTC (^{227}Th)	Bayer	Mesothelin^{+} tumors
aCD33-TTC (^{227}Th)	Bayer	Leukemia
FPX-01 (^{225}Ac)	J&J/Fusion Pharma	NSCLC, pan-cancer target

Radiopharmaceutical therapy

- 21 RPTs
- 5 commercially available/FDA approved
  - ^{131}I thyroid malignancies
  - Xofigo (^{223}Ra) castration resistant prostate cancer bone mets
  - Lutathera (^{177}Lu) somatostatin^{+} tumors
  - Sirtex (^{90}Y) hepatic malignancies
  - Therapsheres (^{90}Y) hepatic malignancies
- 3 beta-emitters – ^{131}I, ^{177}Lu, ^{90}Y
- 4 alpha-emitters – ^{225}Ac, ^{227}Th, ^{212}Pb/^{212}Bi, ^{223}Ra

Emission types in RPT

alphas

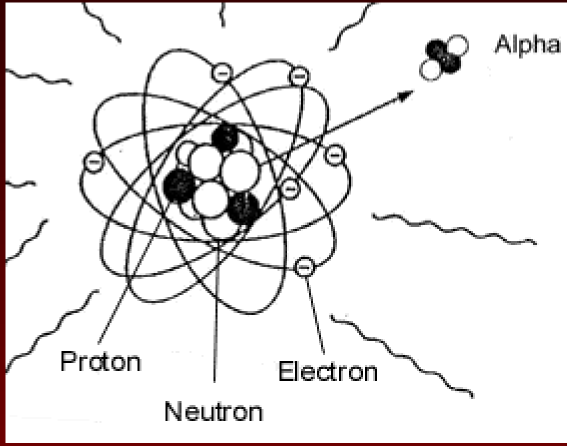
- He nucleus
- 80 keV/μm
- 2 to 3 tracks kill cell
- Irrepairable DNA damage
- potent single cell, cluster kill

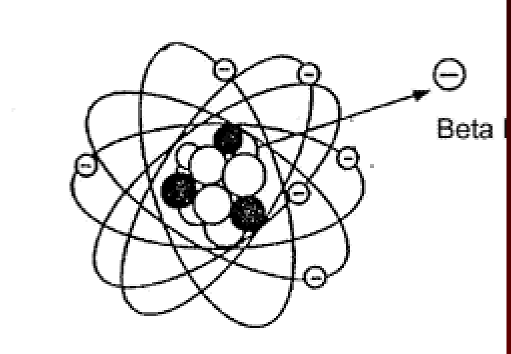
betas (electrons)

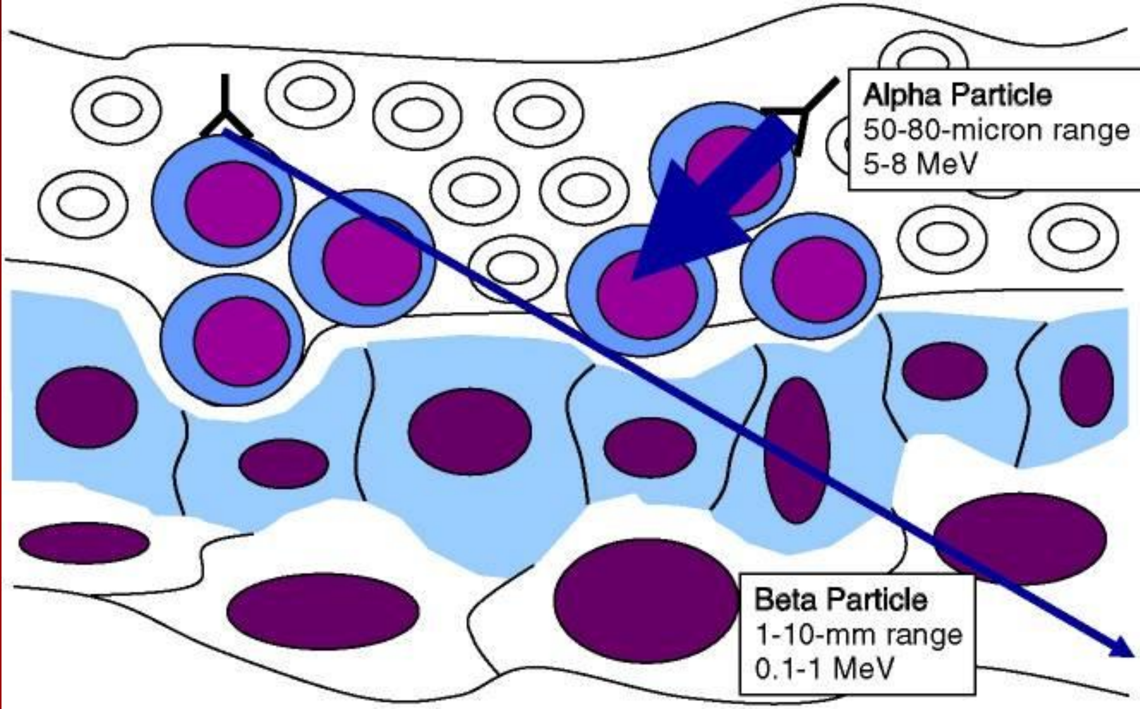
- elem particle
- 0.2 keV/μm
- 10^3 to 10^4 tracks to kill cell
- DNA damage is repaired
- cross-fire required

photons

- used for imaging



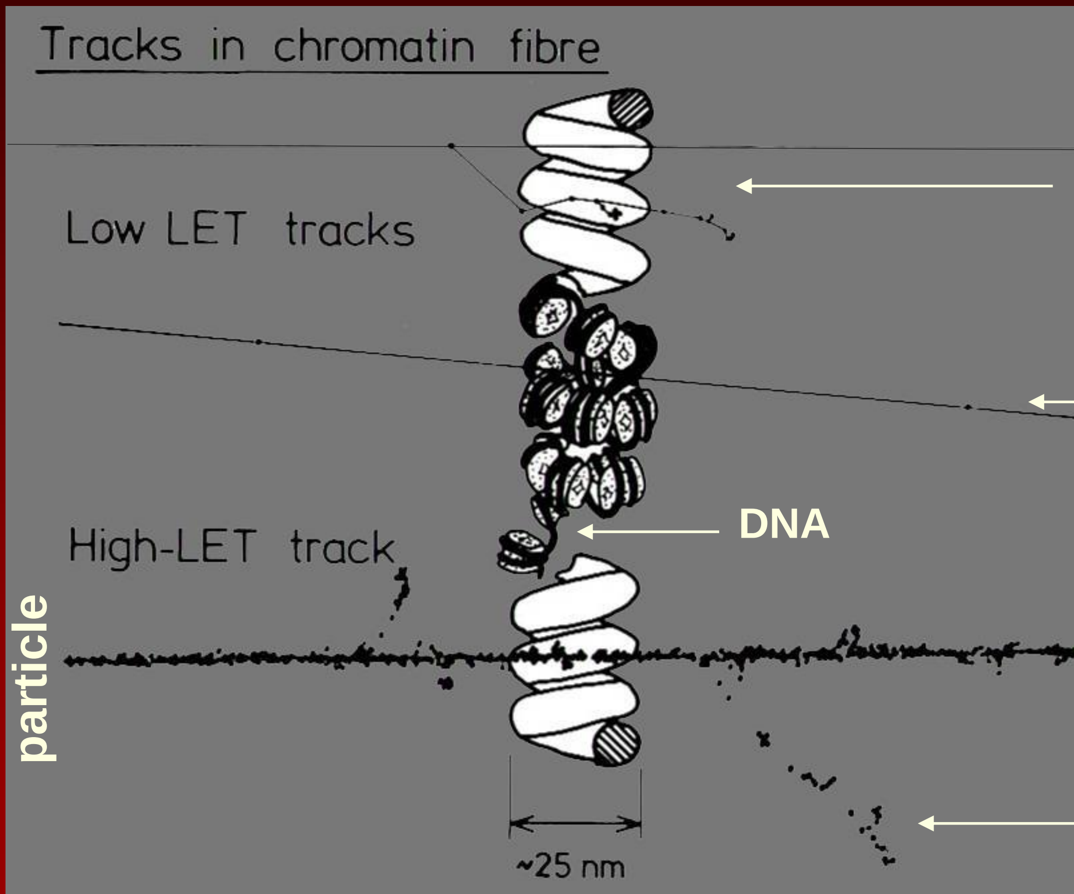




Linear Energy Transfer (LET)

electrons

Alpha-particle



Clustered ionizations from low-energy electron

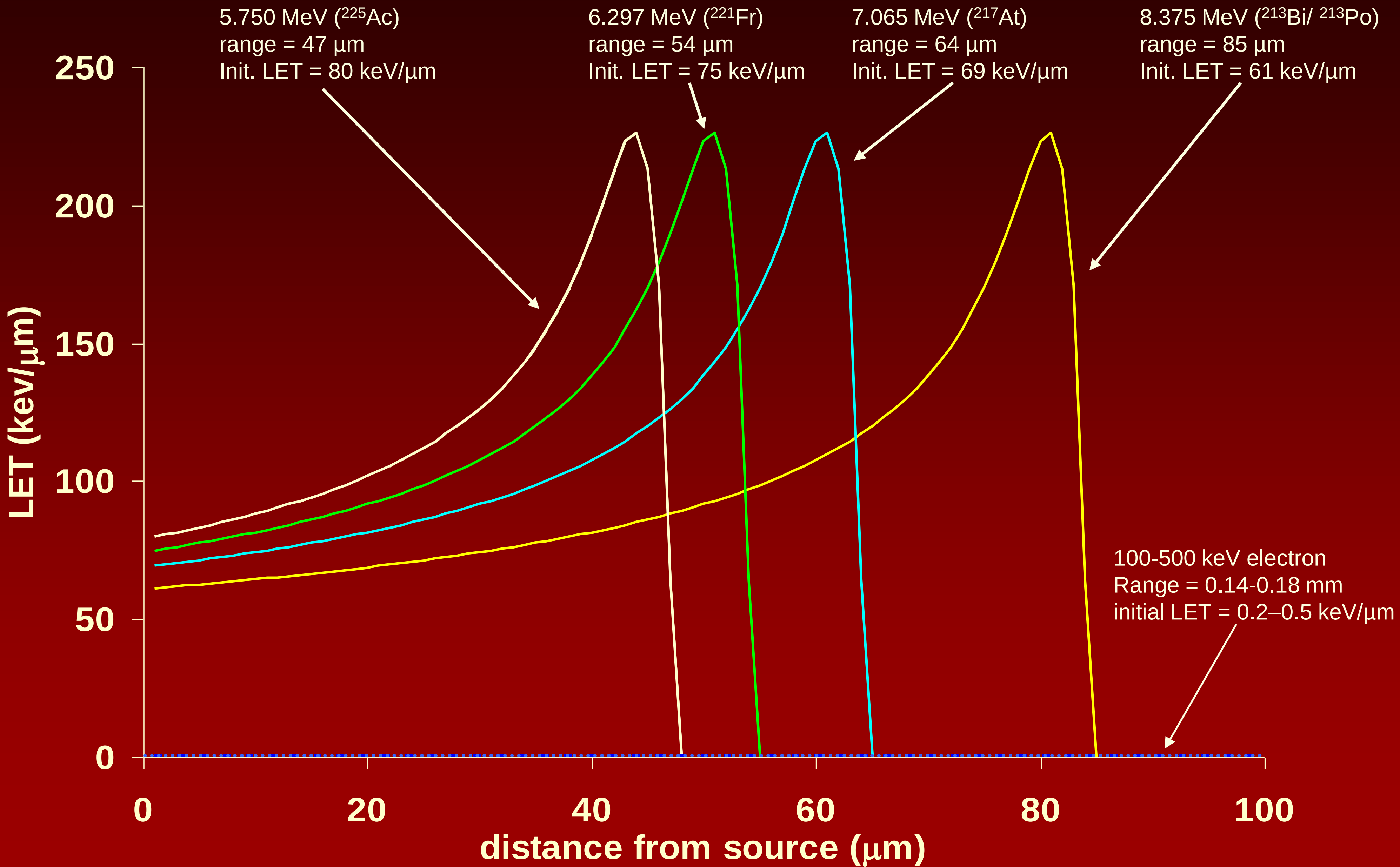
Single ionization

-- high probability of damage when alpha-particle hits DNA.

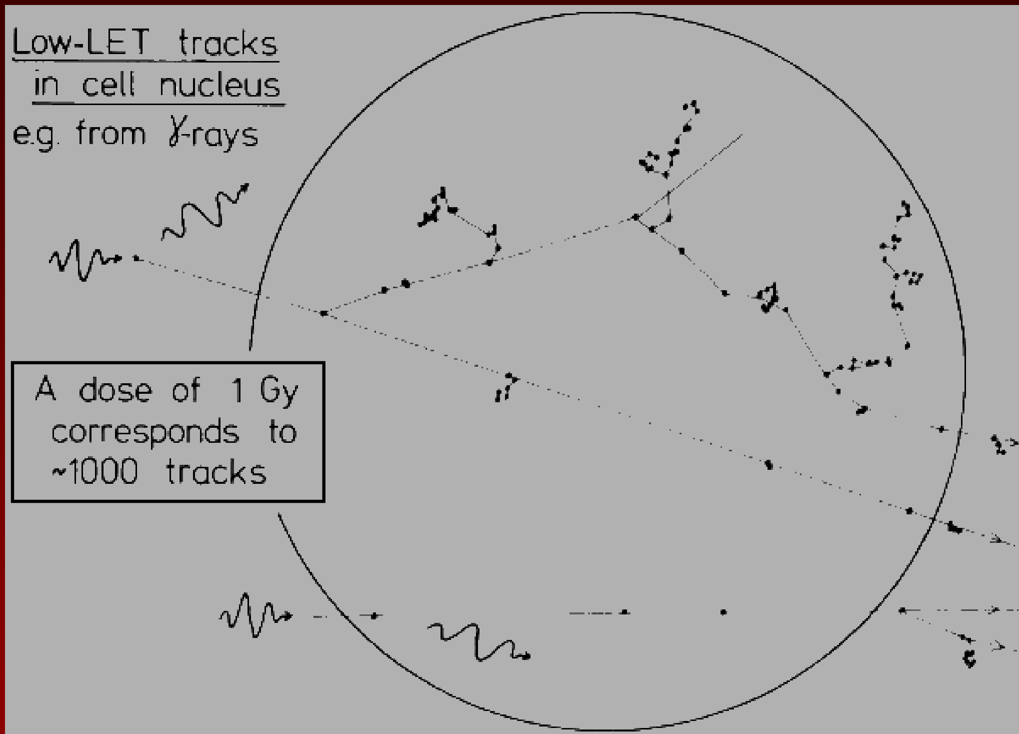
Delta-ray electron

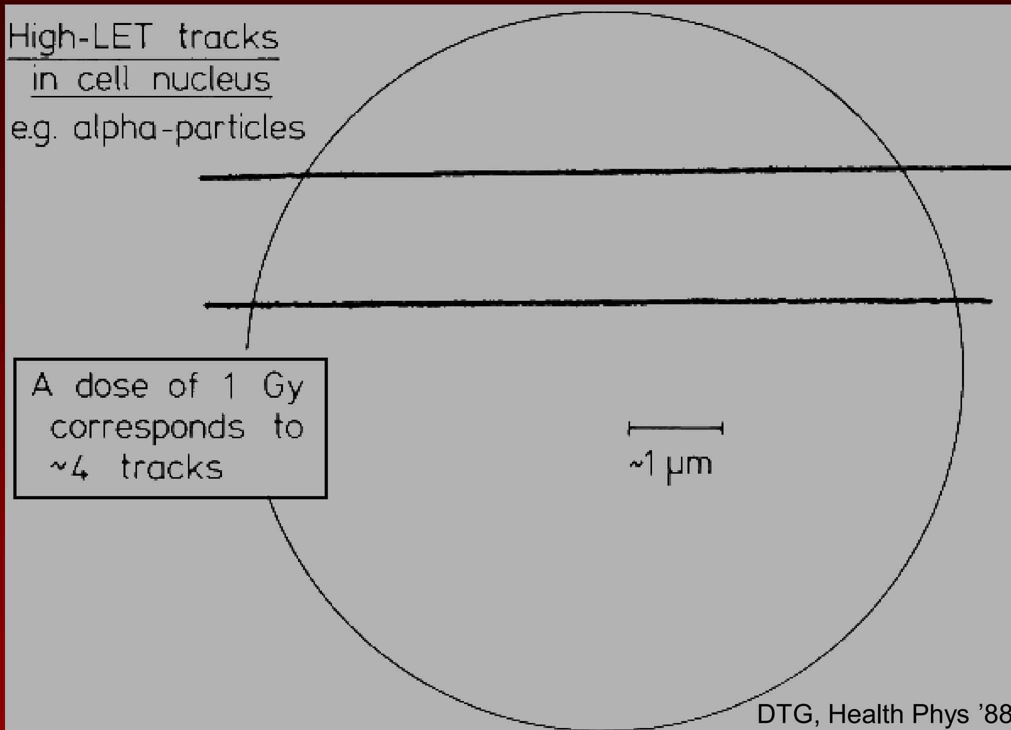
(D.T.Goodhead, CERRIE Workshop 2003)

Linear Energy Transfer – Ac-225



Alpha Radiobiology

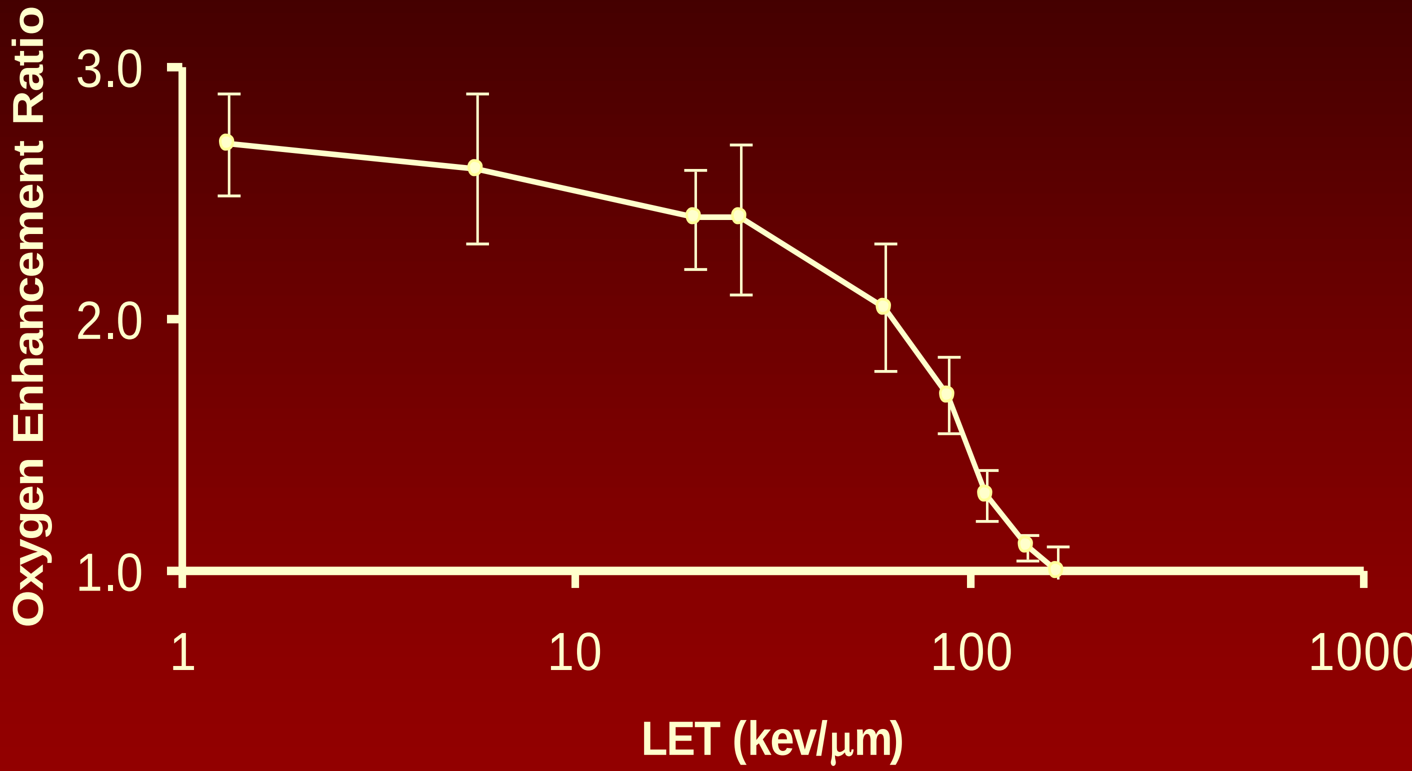




- e^- dose deposition is more uniform but less potent
- ~250 x more e^- tracks needed

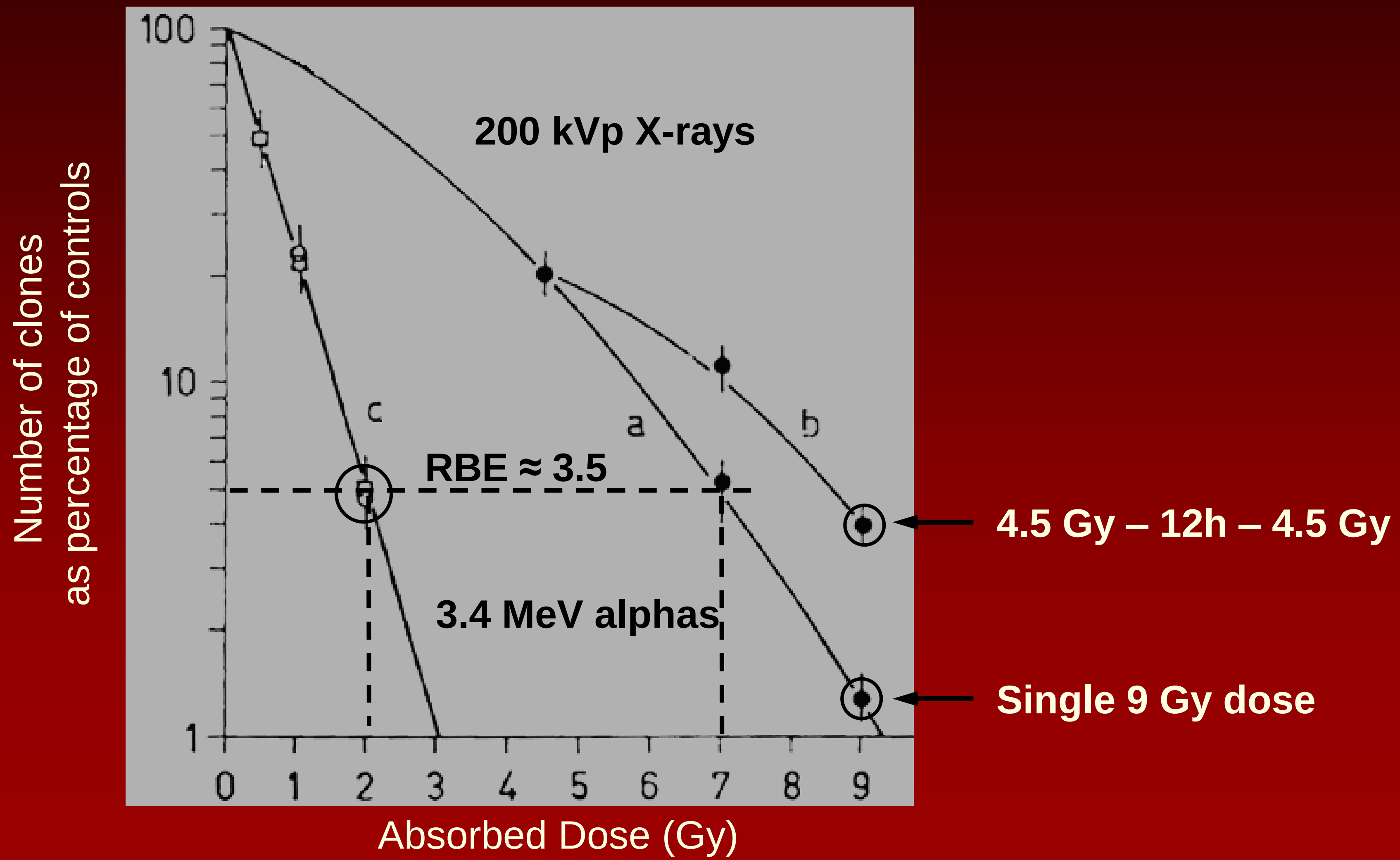
Reduced oxygen effect

$OER = D_{hypoxic}/D_{oxic}$



(Barendsen, et al., Int J Radiat Biol 10:317-3

No dose-rate/fractionation effect



Barendsen GW., 1964

Relative Biological Effectiveness (RBE)

- **dose for cell kill w/ betas ≈ 3-7 x alphas, *in vitro***

$$RBE(x) = \frac{D_r(x)}{D_t(x)}$$

x = biological effect,
r = reference radiation,
t = test radiation

- **RBE influenced by:**
  - **Biological end-point**
  - **Reference radiation**
  - **Dosimetry methodology**

Radiobiology of different emissions

Radiation "type"	Relative Biological Effectiveness (RBE)
X-rays	1
Gamma Rays	1
Beta Particles	1
Alpha Particles	3-7

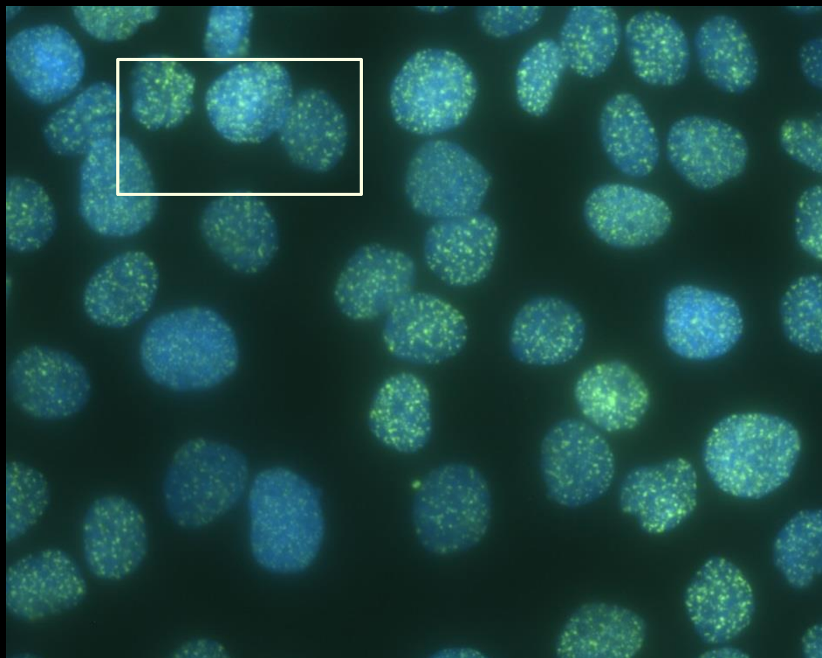
Radiobiology of different emissions

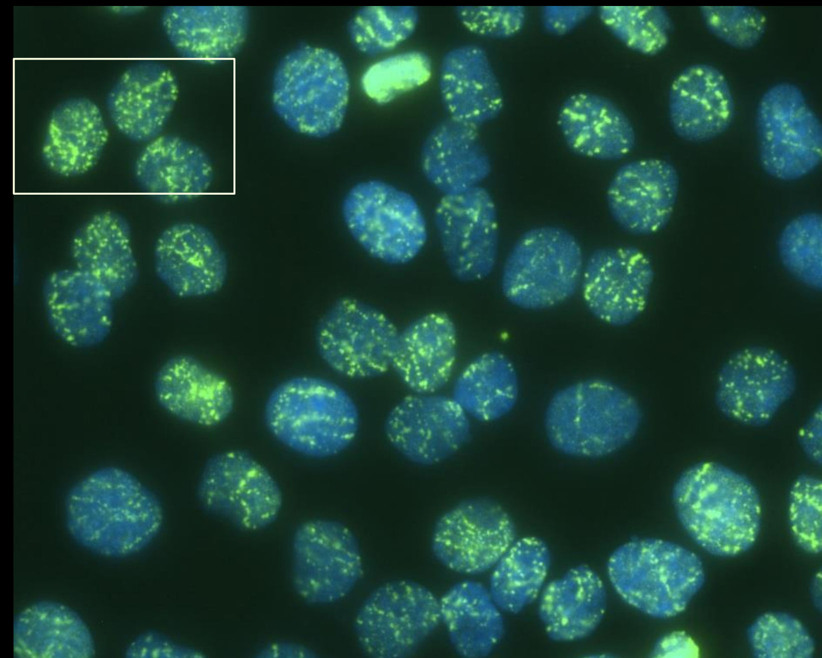
Literature RBE List taken from refs.			
Radionuclide	end-point	reference radiation	RBE
^{213}Bi (Fab')	MTD	^{90}Y (Fab')	≈1
^{213}Bi (Fab')	TGD*	^{90}Y (Fab')	2-14
^{211}At (IgG)	WBCR	whole-body ^{60}Co	5.0 ± 0.9
^{211}At (IgG)	WBCR	^{99m}Tc (F(ab')$_2$)	3.4 ± 0.6
^{211}At (F(ab')$_2$)	TGD	whole-body ^{60}Co	4.8 ± 0.7
^{213}Bi (IgG)	ND	^{90}Y (IgG)	≈1
^{213}Bi (IgG)	LR	^{90}Y (IgG)	≈1
^{227}Th (IgG)	TGD	^{90}Y (IgG)	5.5
^{227}Th (IgG)	TGD	X-rays	2.5-7.2
^{227}Th (IgG)	50%, 100% TGD	^{177}Lu (IgG)	2.8, 2.2

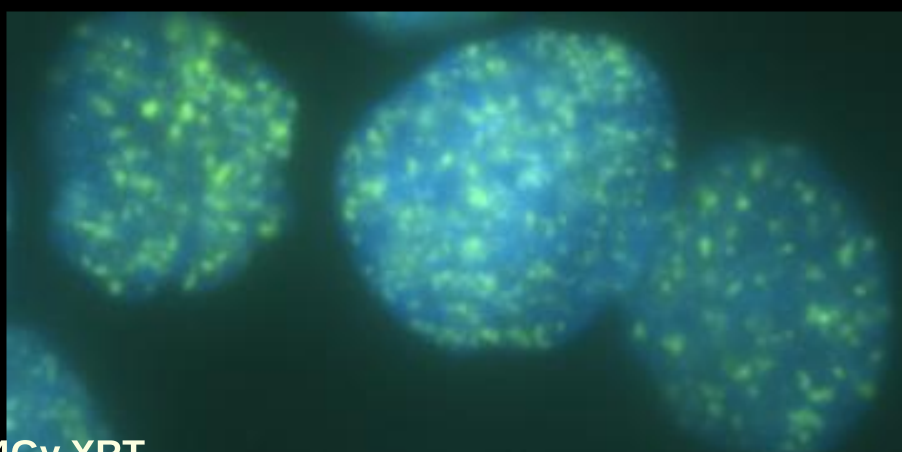
***TGD = tumor growth delay; WBCR = white blood cell reduction; ND = nadir duration; LR = leukemia reduction**

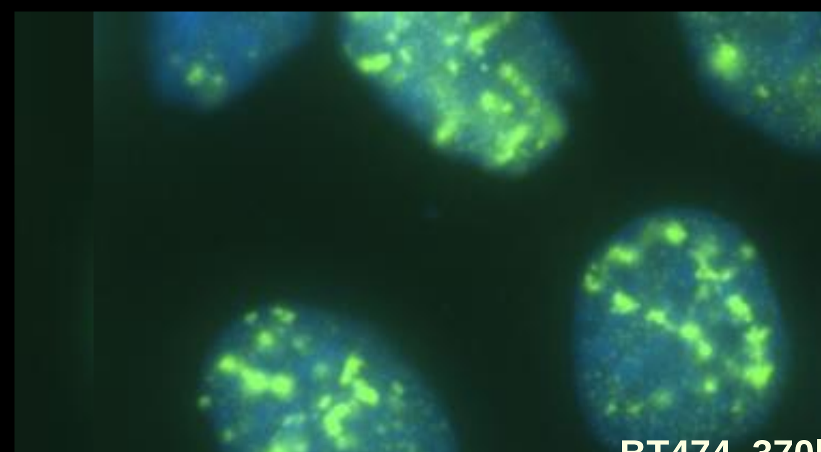
MIRD Committee Alpha monograph, 2015

DNA double-strand breaks









BT474, 4Gy XRT
@1h

BT474, 370kBq (10 uCi)
^{213}Bi-trastuzumab @1h

Repair, Radiosensitization and RBE

1 hr 24 hr 1 hr 24 hr

Radiosensitivity (D_0) and relative biological efficacy (RBE) of the MDA-MB-231cell line under different exposure and DNA repair pathway inhibition conditions.

Agent, manipulation	D_0 (Gy)	RBE*
^{213}Bi-Rituximab (irrelevant Ab)	0.84	3.8
^{213}Bi-Cetuximab	0.87	3.7
^{213}Bi-Cetuximab, siRNA scrambled control	0.69	4.7
^{213}Bi-Cetuximab, siRNA DNA-PKcs-/DNA-PKcs-	0.37	8.6
^{213}Bi-Cetuximab, siRNA BRCA1-/BRCA1-	0.21	15.6

*RBE is reported using 37% cell survival as the biological endpoint and Cs-137 gamma rays as the reference radiation.

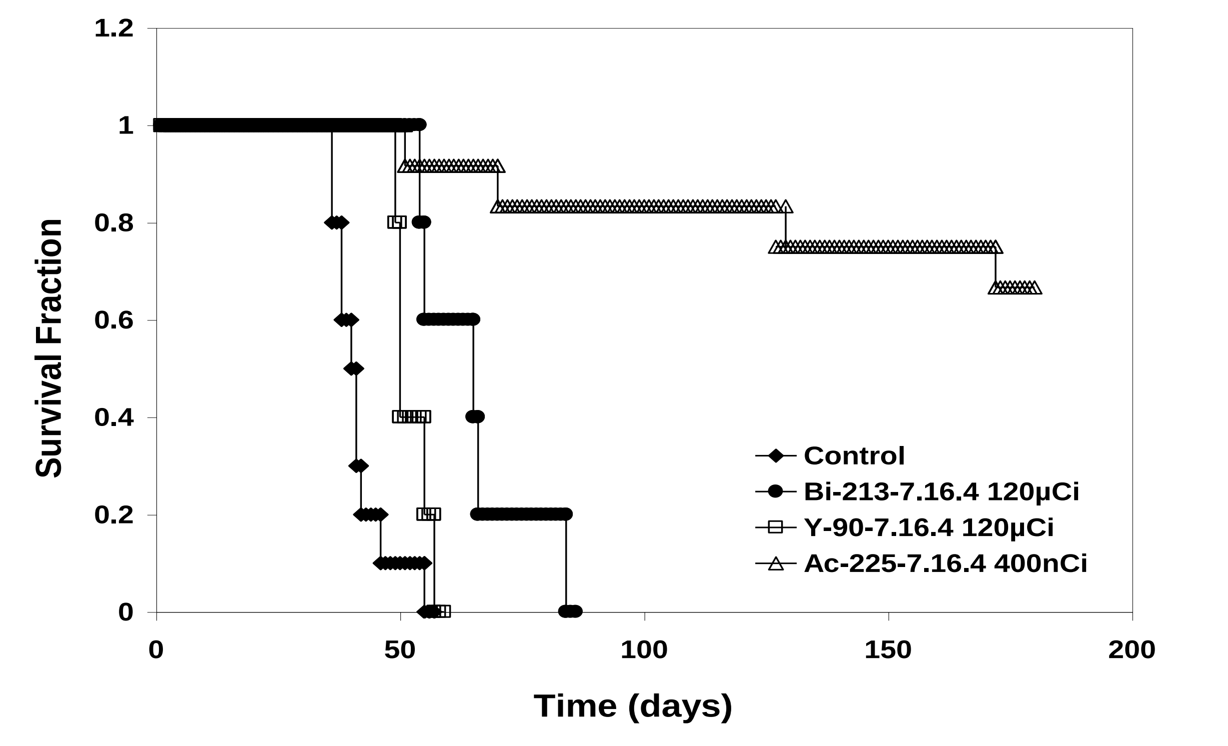
0 2 4 6 8 10 12

Cetuximab-Bi213 (μCi/mL)

Song, et al. MCT 2013

Treatment of early stage breast cancer pulmonary metastases

Neu-N mice were treated 3 days after *i.v.* injection of $1x10^5$ NT2.5 breast cancer cells.



Median survival:

Control (n=10): 40.5 days

120 µCi ^{90}Y-7.16.4 (n=5): 50 days

120µCi ^{213}Bi-7.16.4 (n=5): 65 days

400 nCi ^{225}Ac-7.16.4 (n=12): 8/12 surviving

	Control	^{90}Y-7.16.4	^{213}Bi-7.16.4	^{225}Ac-7.16.4
Control	*****	*****	*****	*****
^{90}Y-7.16.4	*P* =0.01	*****	*****	*****
^{213}Bi-7.16.4	*P* =0.002	*P* =0.04	*****	*****
^{225}Ac-7.16.4	*P* <0.0001	*P* <0.0001	*P* =0.0005	*****

Song, et al. Cancer Res '09

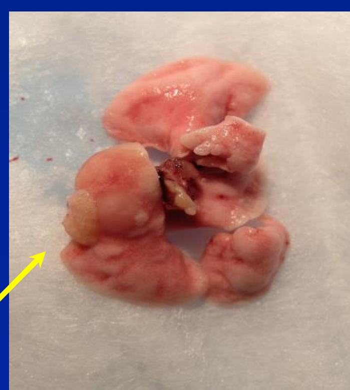
Long term efficacy and toxicity of 7.16.4-^{225}Ac treated *neu*N mice

One year after treatment, surviving mice were sacrificed.

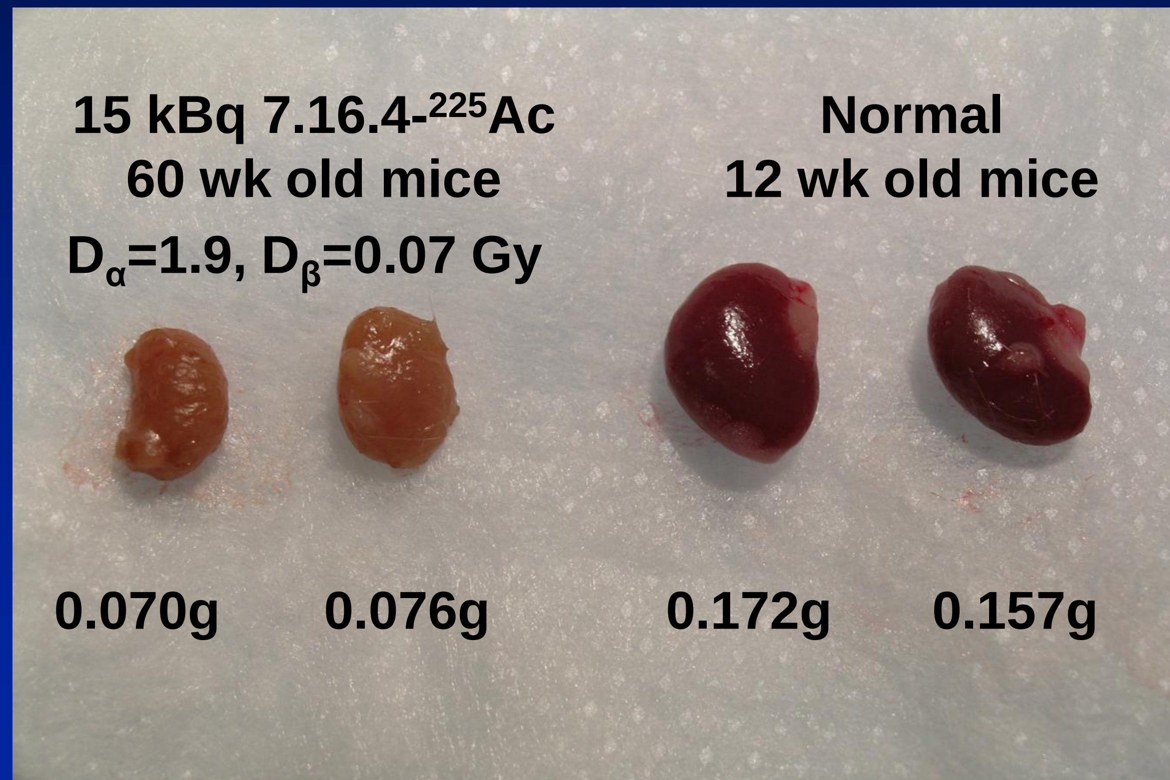
Lungs

15 kBq (400 nCi)
7.16.4-^{225}Ac

7.5 + 7.5 kBq
7.16.4-^{225}Ac

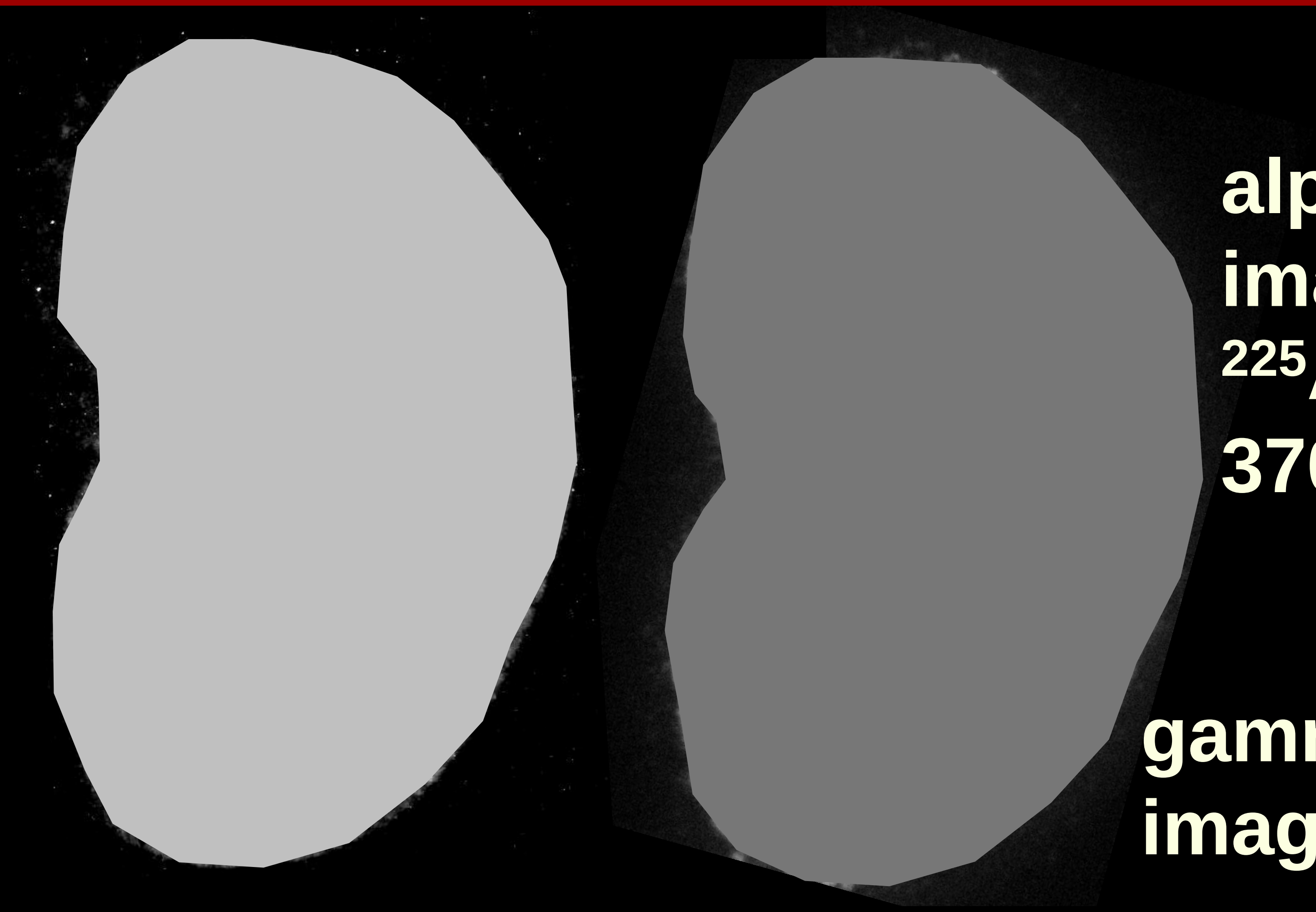


Kidneys



Song, et al. Cancer Res '09

Kidney dosimetry



30 min PI

6 days PI

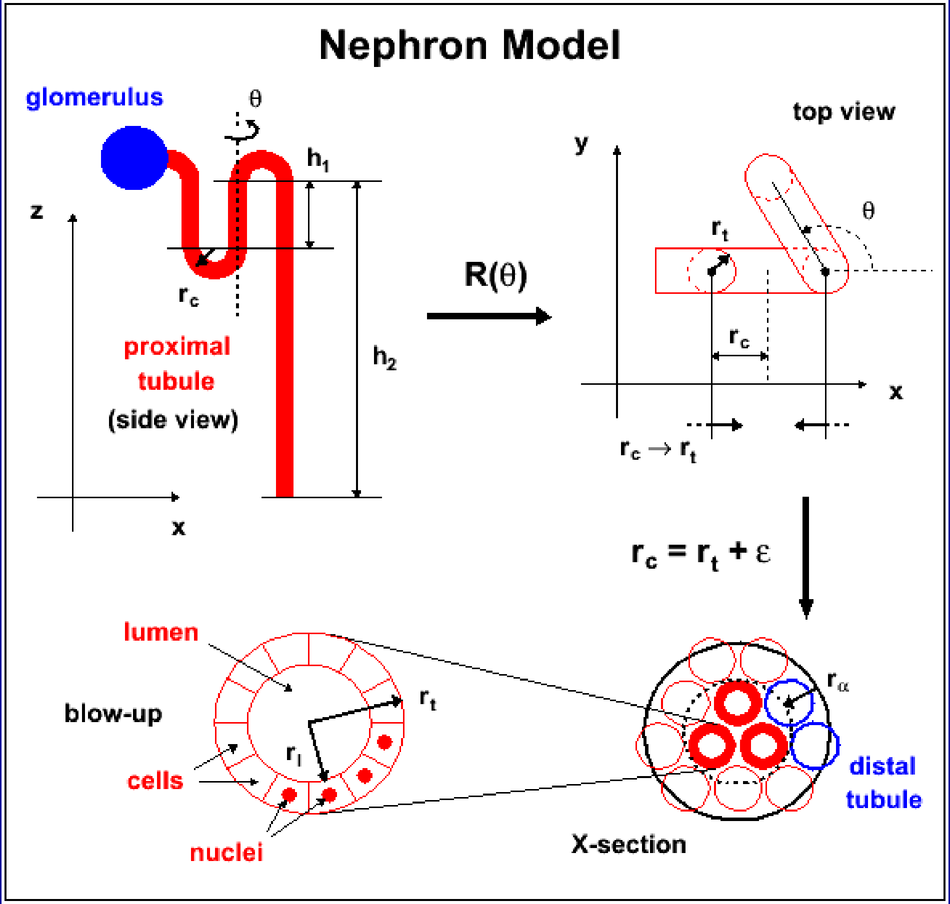
alpha-camera images, IV, ^{225}Ac-Ab 370 kBq

gamma-camera images

Nephron Model

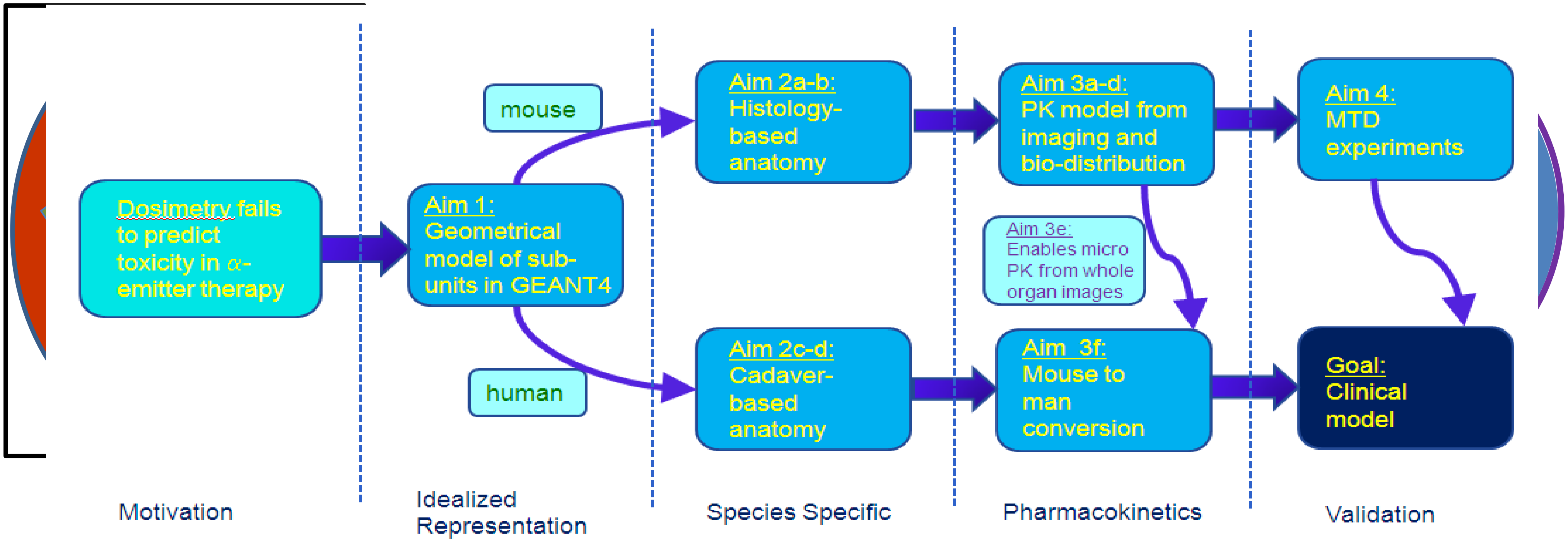
Use simple geometrical shapes á la MIRD (spheres, toroids cylinders) and literature values

1. Fold tubules to simulate proximity
2. Discriminate between tubule cells (simple cuboidal epithelials) and lumina
3. Consider range of α's and ratios of proximal/distal neighbors



Hobbs *et al.* Phys Med Biol '12

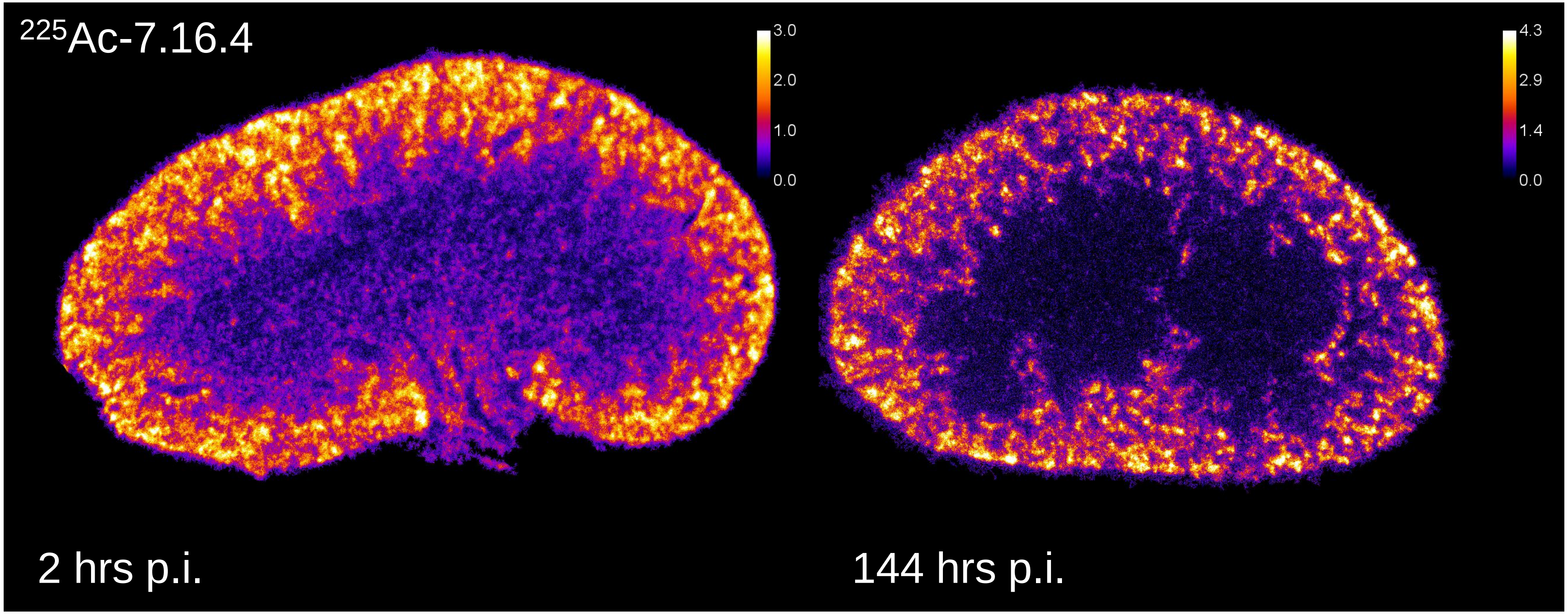
Macro to Micro Modeling



Hobbs, et al. Phys Med Bio '12

Results

α-Camera images



Results

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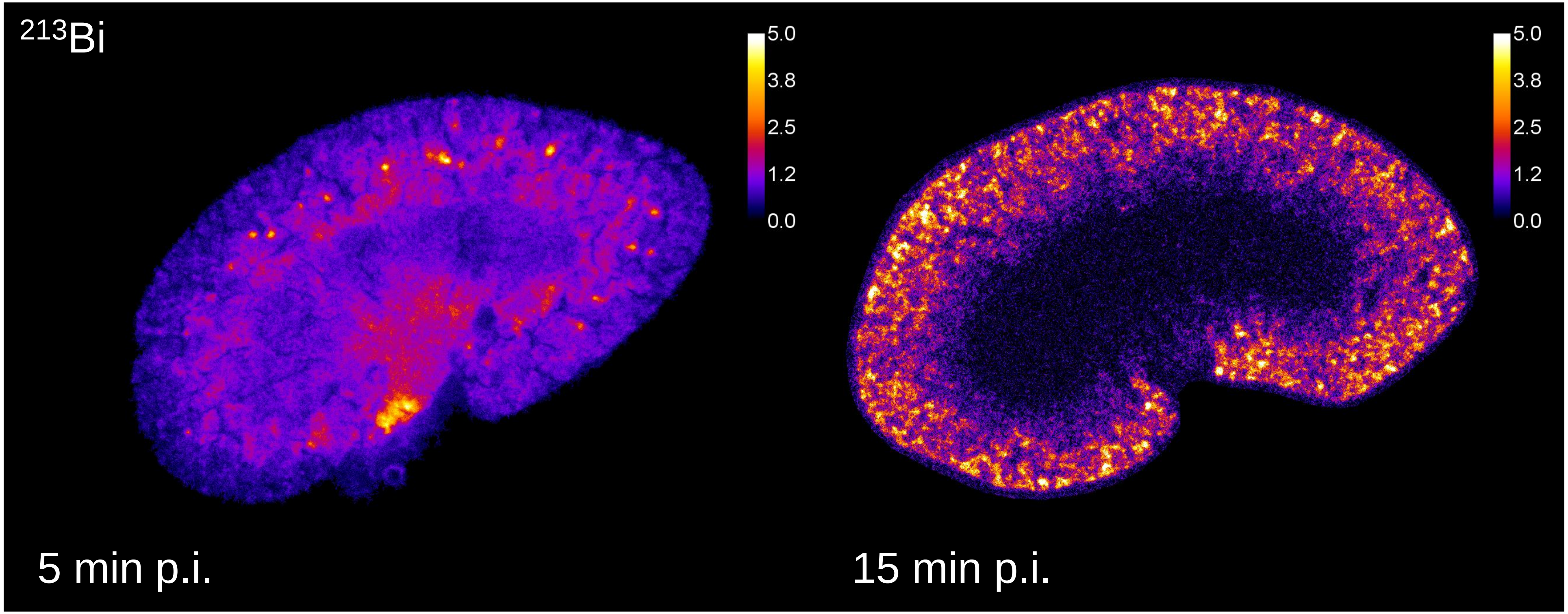
α-Camera images



Murine Histological Input

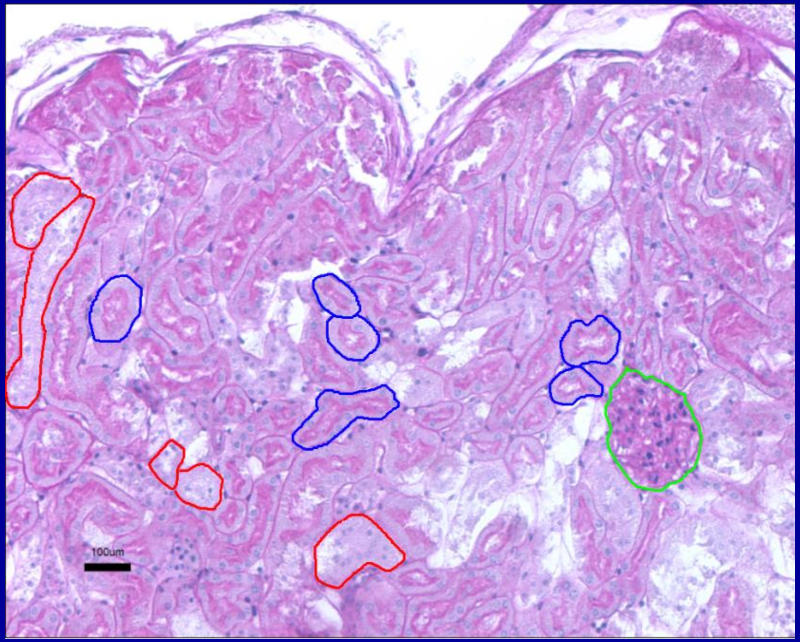
Geometric model supplemented by anatomical data (PAS staining for proximal tubule versus distal tubules)

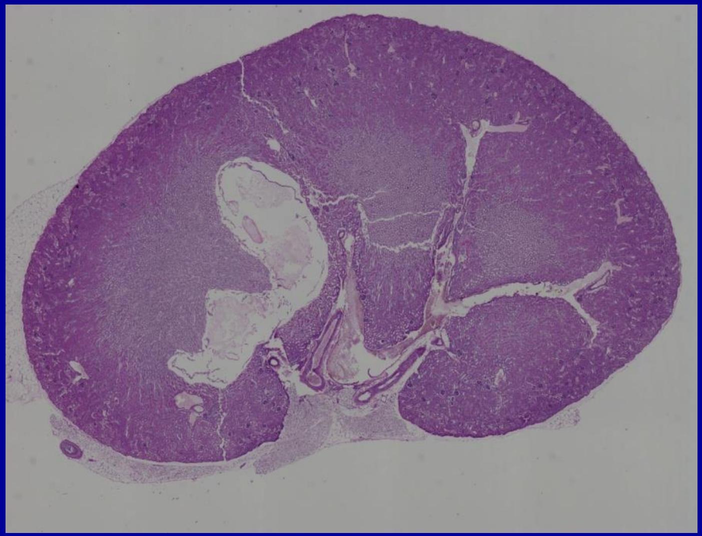
- size and parameters (range of values) for different compartments and cells

Tubule radius: (14 +/- 4) μm
Lumen radius: (4 +/- 2) μm
Glomerulus radius: (65 +/- 20) μm

- fractions of occupancy

Proximal tubule f_i: 81%, 53%
(Proximal tubule cells f_i: 66%, 43%)
Glomerulus f_i: 2.3%, 1.5%





Results

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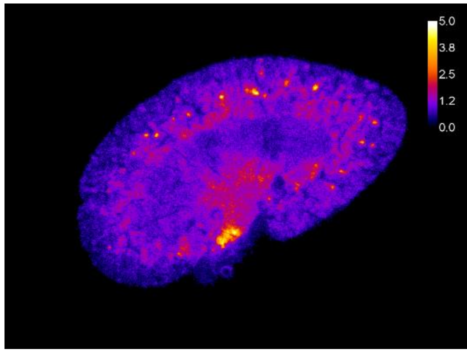
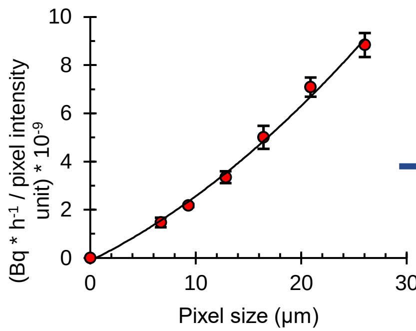
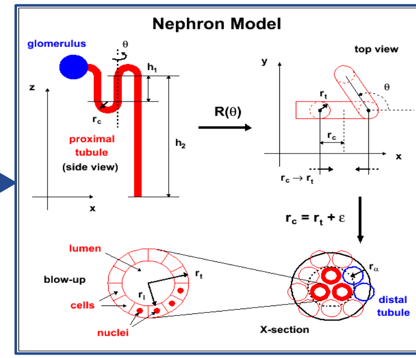
Small-scale dosimetry



α-Camera image



Quantification



Nephron model

Absorbed dose

14.8 kBq ^{225}Ac-7.16.4

	Whole organ dosimetry	Small scale dosimetry
^{225}Ac-7.16.4:	8.1 Gy	Proximal tubules ~3.0-4.3x higher
^{213}Bi:	1.3 Gy	Proximal tubules ~5.0x higher
Total:	9.4 Gy	Proximal tubules ~3.3-4.4x higher

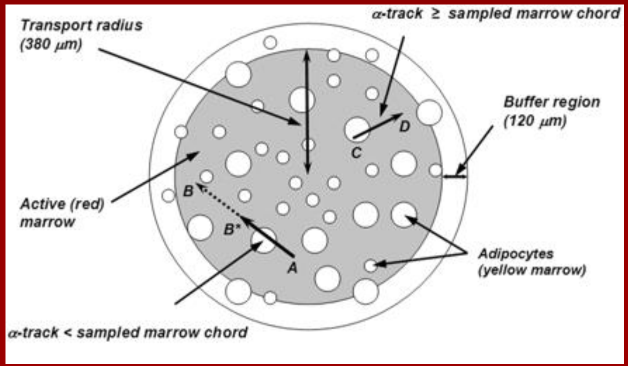
Ra-223 BM dosimetry

Alpharadin: A novel, targeted approach for treatment of bone metastases from CRPC-calculated alpha-particle dosimetry compared to a favorable clinical safety profile.

V. Lewington, et al., ASCO GUI Ca Symp.;2010

- RM absorbed dose ≈ 1 Gy x RBE of 5 = 5 RBE-weighted Gy
- Less than 1% of 292 patients had CTC grade 4 hematological toxicity; 2%-4% had grade 3 toxicity for hemoglobin, platelets, neutrophils or WBC.

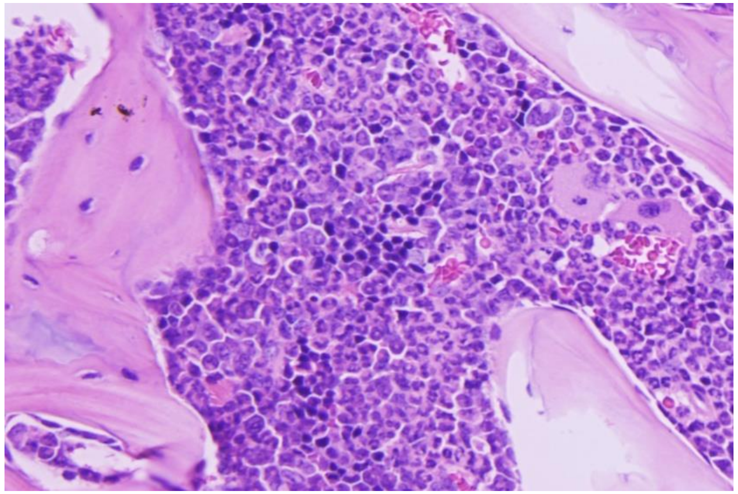
$$D_{TAM} = \tilde{A} \cdot S(TAM \leftarrow TBS)$$



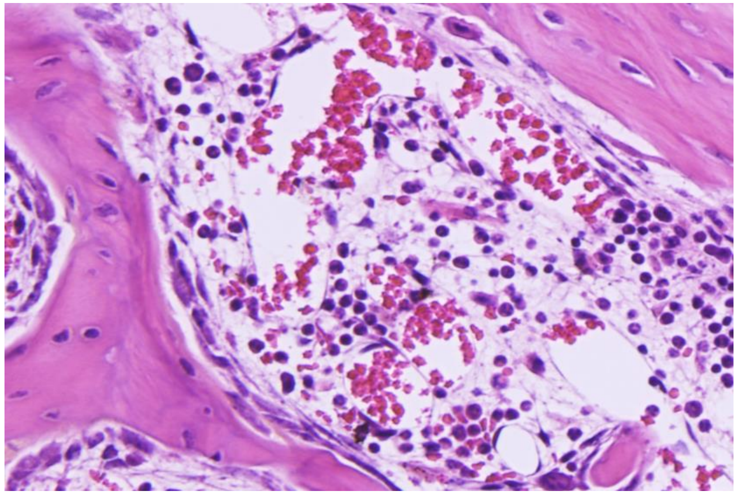
Watchman, *et al.* JNM '05

BM toxicity

Normal



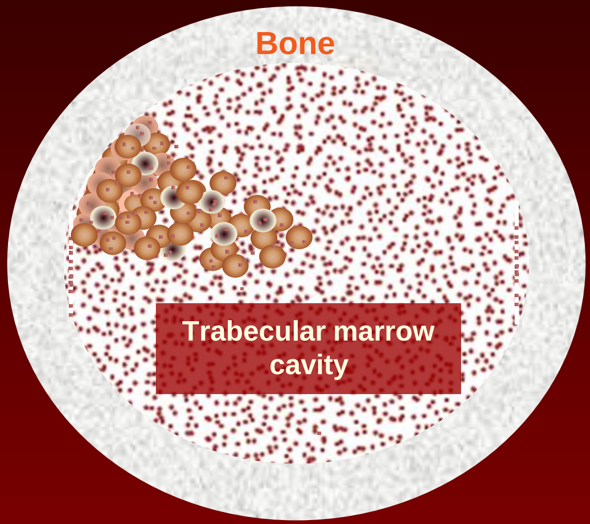
24 hr post120μCi ^{213}Bi-7.16.4



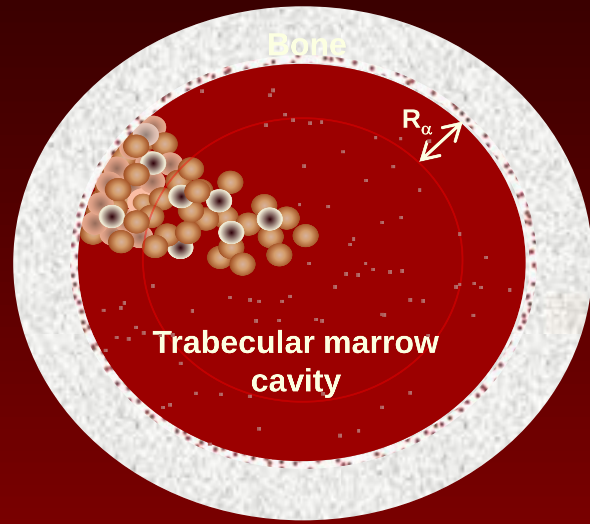
Histopathology H&E staining of bone marrow in normal *neu*N mice and one day after injection of 120μCi ^{213}Bi-7.16.4. Depletion of lymphocytes can be clearly seen in bone marrow, although small fraction of lymphocytes are still remaining, which are able to repopulate marrow.

Song, et al. Cancer Res '08

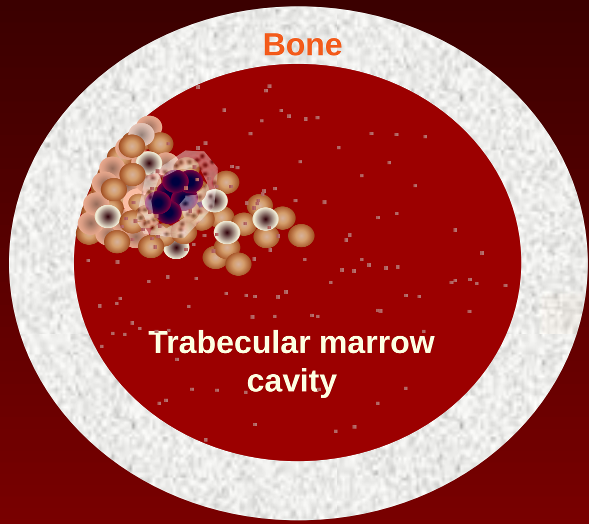
Dosimetry



- Alpha-emitters uniformily distributed
- If target cells are also uniformly distributed
- Mean to cavity will reflect biological effects



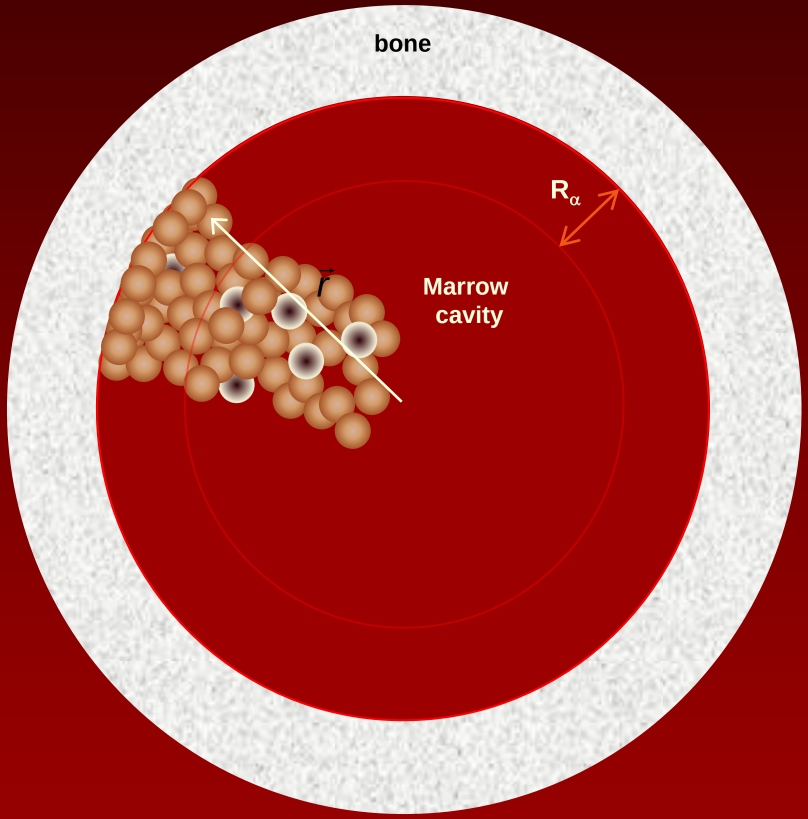
- Alpha-emitters mostly on bone surface
- Mean to marrow cavity won’t predict effect

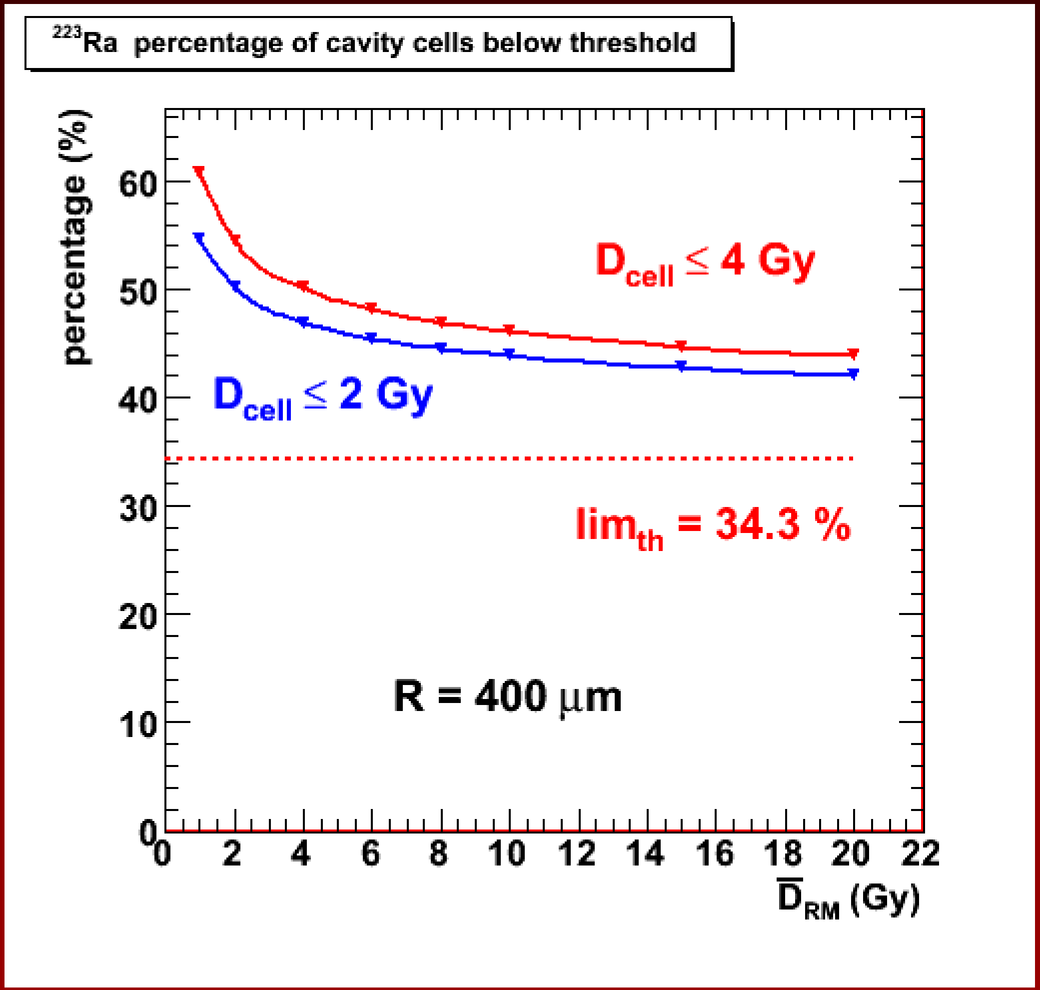


- Alpha-emitters mostly on target cells in marrow
- Mean to marrow cavity won’t predict effect

Hobbs, *et al* Phys Med Bio ’12

Dose-response for toxicity





Hobbs, et al. Phys Med Bio '12

Dose → biological effect

- Tumor control probability (TCP) as function of:
  - Cell number
  - Antigen density
- Impact of Ag density variation
- Used MIRD Cellular S values for ^{213}Bi dosimetry

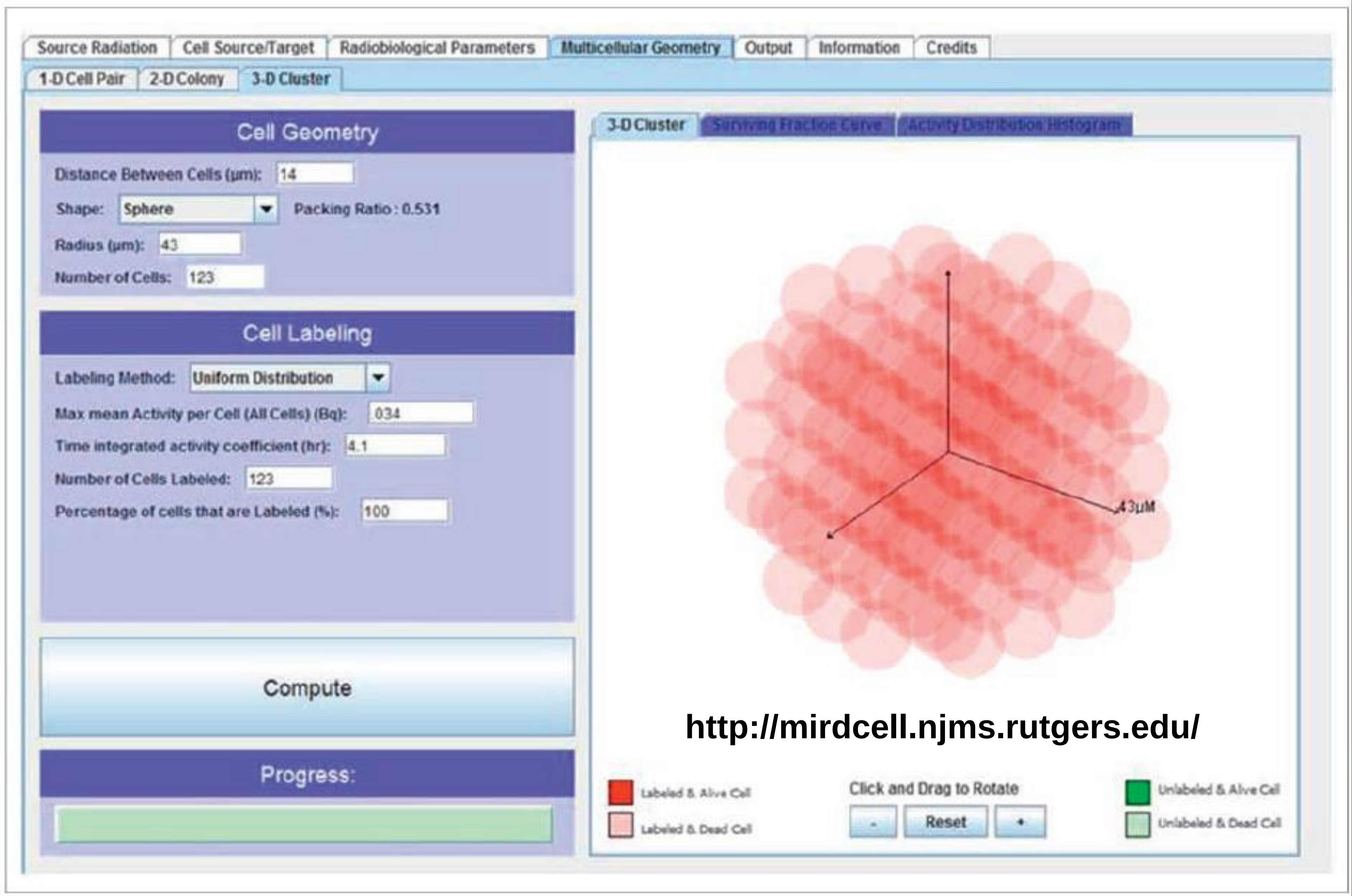
Table 2. Tumor Control Probability (TCP) for Different Target Cells and Two Different Cell-Surface Antigen Densities

	TCP			
n *(cell number)*	*10*	*100*	*1000*	*10,000*
10^5 sites/cell	0.92	0.43	2.2×10^{-4}	2.2×10^{-37}
10^5 sites/cell ± 10%[a]	0.90	0.37	5.3×10^{-5}	1.6×10^{-43}
10^5 sites/cell ± 50%	0.47	1.4×10^{-3}	3.7×10^{-32}	0
2×10^5 sites/cell	1.00	0.99	0.93	0.49
2×10^5 sites/cell ± 10%	1.00	0.99	0.89	0.30
2×10^5 sites/cell ± 50%	0.66	3.4×10^{-2}	2.3×10^{-25}	0

[a]Percent standard deviation for normally distributed antigen density.

Sgouros, Song, CBR '07

MIRDcell



Source Radiation
Cell Source/Target
Radiobiological Parameters
Multicellular Geometry
Output
Information
Credits
1-D Cell Pair
2-D Colony
3-D Cluster
Cell Geometry
Distance Between Cells (µm): 14
Shape: Sphere
Packing Ratio : 0.531
Radius (µm): 43
Number of Cells: 123
Cell Labeling
Labeling Method: Uniform Distribution
Max mean Activity per Cell (All Cells) (Bq): .034
Time integrated activity coefficient (hr): 4.1
Number of Cells Labeled: 123
Percentage of cells that are Labeled (%): 100
Compute
Progress:
3-D Cluster
43µM
http://mirdcell.njms.rutgers.edu/
Labeled & Alive Cell
Labeled & Dead Cell
Click and Drag to Rotate
Reset
Unlabeled & Alive Cell
Unlabeled & Dead Cell

Gray (Gy)

- Energy density
  - Energy absorbed/mass absorbing the energy
- SI unit for rad; 100 rad = 1 Gy
- Strictly defined physics quantity

Radiation Weighting Factor (w_R)

- Biological effects of radiation types
  - Deterministic (acute) effects (toxicity, tumor kill)
    - effect increases with dose
    - higher absorbed doses
    - cancer therapy
  - Stochastic effects (cancer induction)
    - probability of effect occurrence increases with dose
    - lower absorbed doses
    - public/worker exposure
- Dependent on RBE (measured quantity)
- Value determined by Committee (ICRP)
  - review of RBE values
- $Sv = w_R \cdot w_T \cdot Gy$

Sievert (Sv)

- Dose equivalent for stochastic biological effects
  - Radiation protection
  - Incorrect to talk about 100 Sv
- SI designation for rem; 100 rem = 1 Sv
- “special named quantity” not a unit
- 1 Gy alpha radiation = 20 Sv
- 1 Gy x-rays = 1 Sv
- Special named quantity for acute effects?
  - therapy/toxicity
  - Equieffective dose EQD_{XX}
- Report Gy for alphas, photons and electrons separately

Recommendations

- Report abs
- Separately   e
- Keep track   ions
- Surrogate i   cro distribution
    - Validate e   scale
- Pre-clinical   stribution