ALPHA BIO-EFFECT MODELING AND SMALL SCALE DOSIMETRY

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DISCLOSURES

Dividends from licensed PI for Radiopharmaceutical Imaging and Dosimetry, LLC (RAPID)

Advisory Board member for Novartis/AAA

Consultant for Varian, Vivos, Boston Scientific, Mirion, AstraZeneca

AAPM chair of RPTSC

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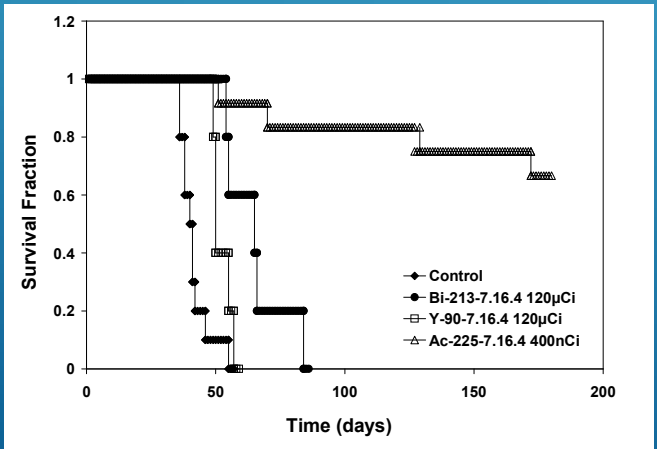
^{225}AC-7.16.4 TREATMENT OF PULMONARY METASTASES FROM BREAST CANCER

Murine tail vein injection, 10^5 NT2 cells, lung metastasis, 5 wks, 100%. [a]

Therapy: effective BUT renal toxicity despite "low" dose [b]

Calculated 2+ Gy to kidneys (typical toxicity thresholds ~40 Gy BED)



[a] **Song** ***et al.*** Clin Cancer Res '08
[b] **Song** *et al.* Cancer Res '09

ALPHA-PARTICLE DOSIMETRY

Can we apply RPT dosimetry (whoe organ or voxelized) paradigms to αRPT?

5 Challenges:

1. **RBE (standardization, variability of parametrization) value of ~5, but could vary**
2. **sub-organ localization of activity – short range means higher dose concentration**
3. **re-localization of daughters (^{225}Ac chain has 4 α-emissions, with ^{213}Bi 45 min HL)**
4. low count rate for imaging (typical therapeutic activity is 100 μCi – few mCi)
5. stochastic energy deposition – recourse to microdosimetry and probability distributions particularly for tumors.

RELATIVE BIOLOGICAL EFFECTIVENESS

RBE definition:

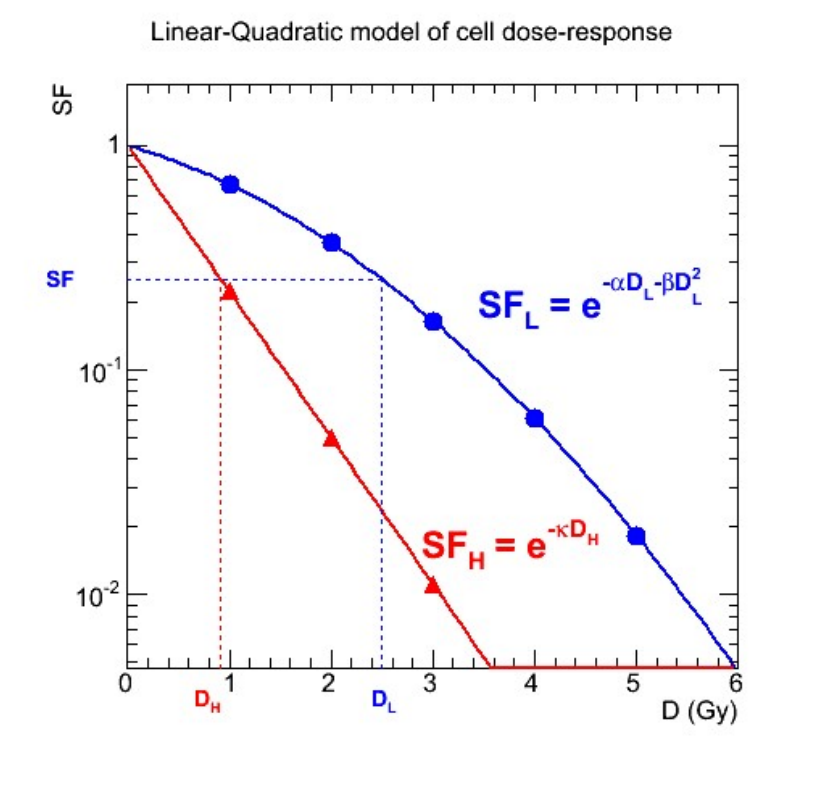
$$RBE = \left.\frac{D_L}{D_H}\right|_{SF}$$

Low-LET response

$$SF = e^{-\alpha_L D_L - \beta_L D_L^2}$$

Alpha response:

$$SF = e^{-\kappa D_H}$$



Hobbs et al. Radiation Res '14

STANDARDIZED RBE (SRBEX)

RBE definition:

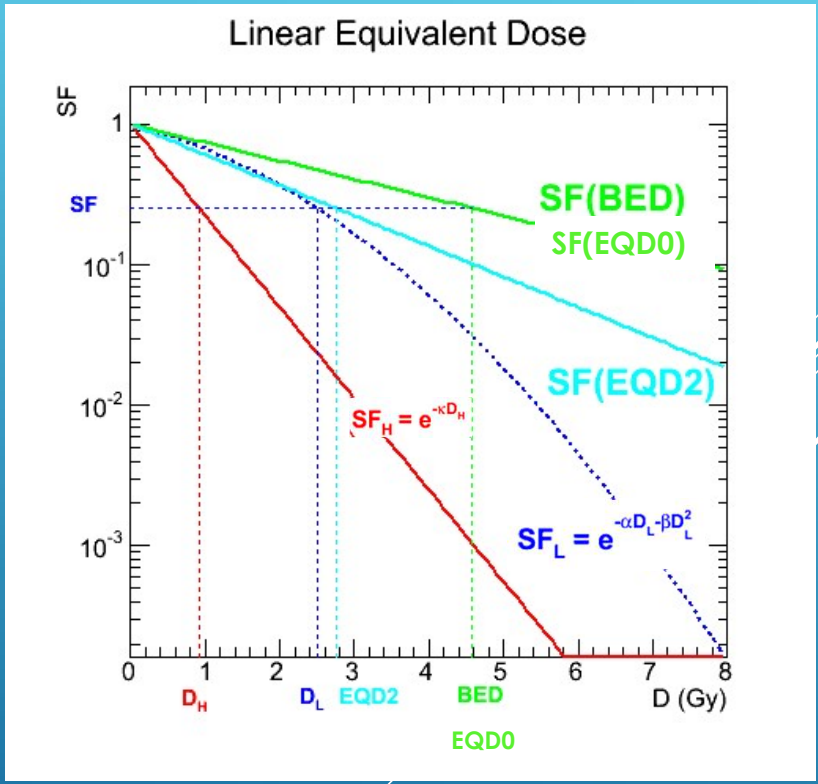
$$RBE = \frac{D_L}{D_H}\bigg|_{SF}$$

A lot of RBEs in the literature with different reference doses. Use the reference EQDX and redefine RBE [a].

ICRU Report 96 has adopted this formalism Ratio is now called sRBEX [b]:

$$sRBEX = \frac{\kappa}{\alpha + \beta X}$$

Eliminates artificial dose dependency



[a] Hobbs *et al.* Radiation Res '14
[b] ICRU Report 96 '21

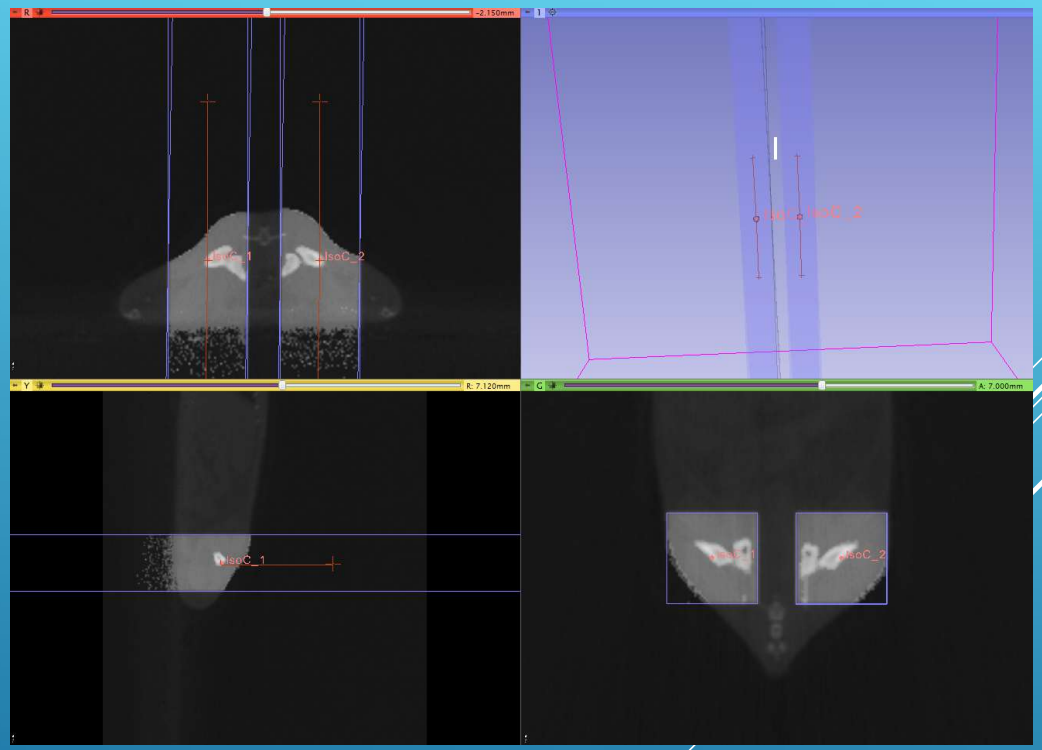
IN VIVO RBE

Design: EBRT 4 Gy fractions to look for biomarkers, metrics of toxicity

Toxicity as a function of αRPT – (Pb-212)

Bone marrow, SG, kidneys (late versus early toxicities and markers)

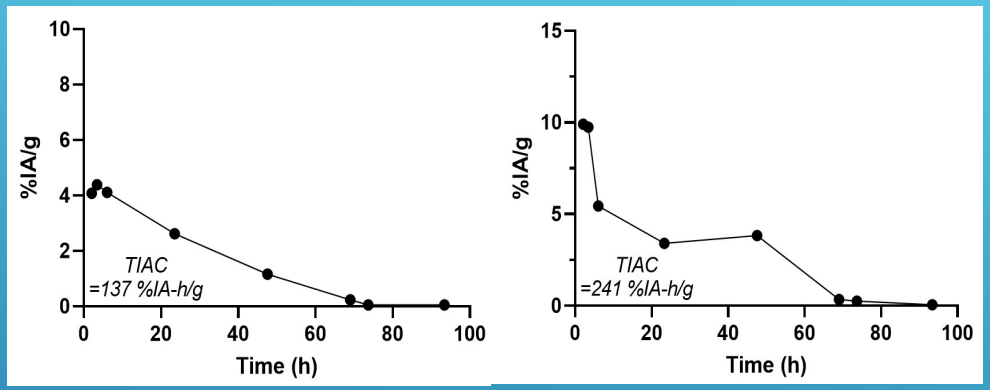
Bone marrow, cellularity reaches a nadir 5 days after irradiation



SARRP (Small Animal Research Radiation Platform

[a] Liatsou et al. Int J Radiat Biol. 2023
[b] Liatsou et al. Int J Radiat Biol. 2024

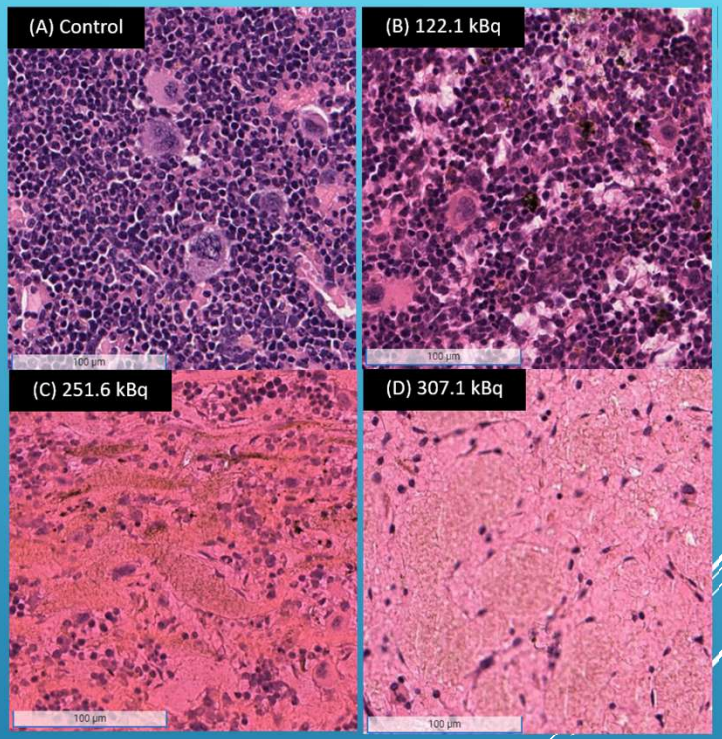
In vivo bone marrow model



Time integrated activity curves of ^{212}Pb-TCMC-7.16.4 in the femur and bone marrow of female *neu*/N mice treated with (122.1-921.3) kBq/10 µg (n = 3/group). Area under the curve was determined for each organ using the log-linear trapezoidal method and the average %IA/g for the same time-points, as shown in the right-hand figure of each panel.

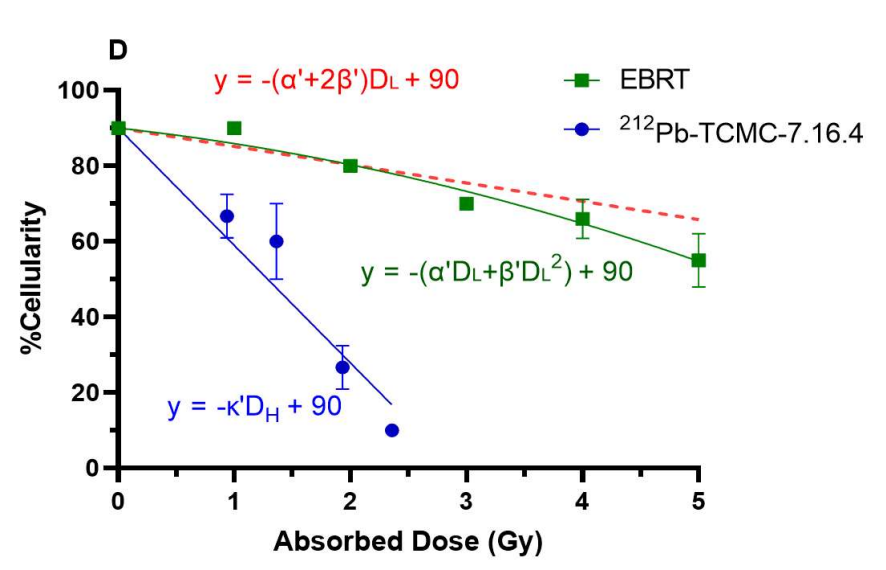
Small scale modeling of bone marrow converts TIAC to dose coefficients

$$D = TIAC \times S$$



Decalcified femur sections post-hematoxylin and eosin staining. Representative histology of **(A)** non-treated control and **(B-D)** mice treated with (122.1, 251.6 and 307.1) kBq/10 µg of ^{212}Pb-TCMC-7.16.4 on the day-3 of nadir (20x magnification).

IN VIVO RBE RESULTS



Administered Activity (kBq)	% Average Cellularity of Femur Region (STD)
0	90.0 (0)
122.1	66.7 (5.8)
177.6	60.0 (10.0)
251.6	26.7 (5.8)
307.1	10.0 (0)
921.3	10.0 (0)

$$RBE2 = \frac{\kappa'}{a'+2\beta'} = 6.4$$

Biological endpoints for other organs remain elusive.
Ongoing efforts for salivary glands and kidneys

RPT-TEC

Alpha group to look at RBE data and try to extract sRBEX data

Advocates using raw AD values. MIRD Pamphlet #22 lists doses from different source independently.

FDA wants BED values, but most RBEs are not defined with respect to BED (sRBE0), but likely within a sRBE0 – sRBEX range. Using the generic value of 5 doesn't bring anything new to the value (as opposed to the linearization to the BED for beta RPTs) and will confuse things if this is claimed to be the BED, which will likely be the case.

Do whole organ AD (for alphas, organ-level BED for betas)

Small scale dosimetry data will be developed that will take user-input organ-level time activity data and provide organ-level RPT-specific dosimetry and biologically standardized (EQDX) small scale dosimetry.

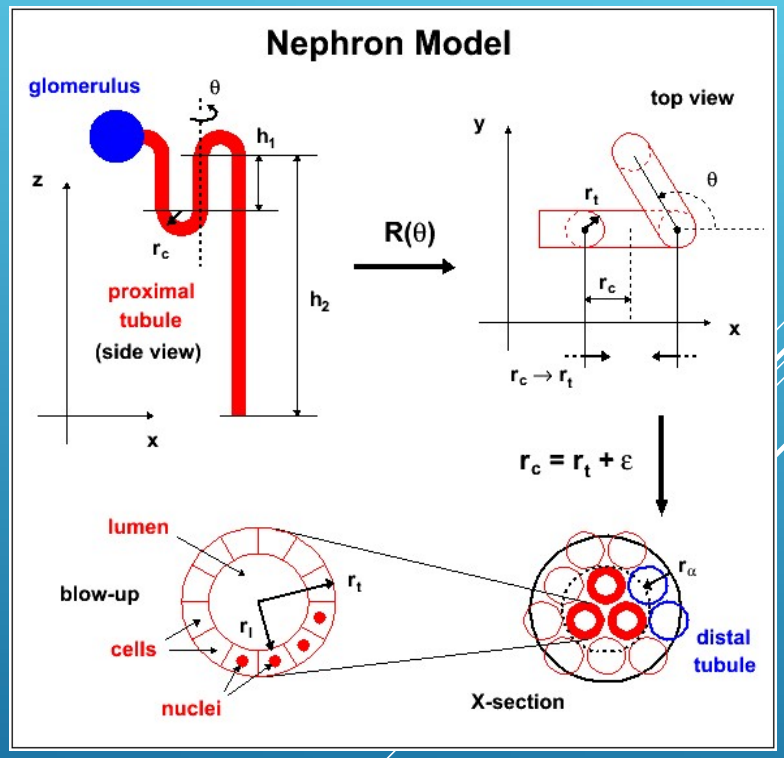
NEPHRON MODEL

$$D_i = \sum_j S_{i \leftarrow j} \cdot \tilde{A}_j$$

Short range of Alphas – localized uptake driven by physiology results in non-uniform absorbed dose distribution. Adapt absorbed fraction to small scale!

Use simple geometrical shapes (spheres, toroids cylinders) for S-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
4. Run MC for S values

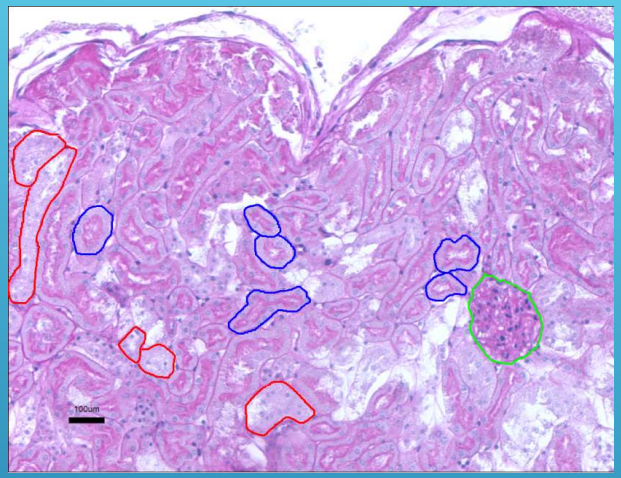


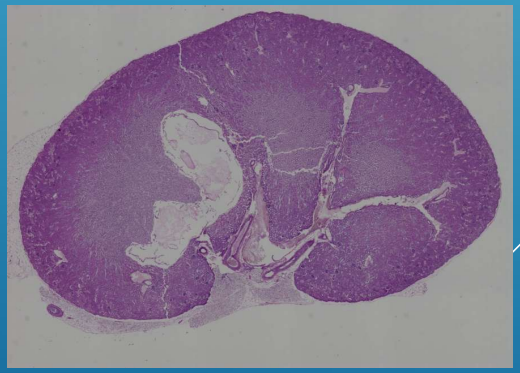
Hobbs *et al.* Phys Med Biol '12

(MURINE) HISTOLOGICAL INPUT

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

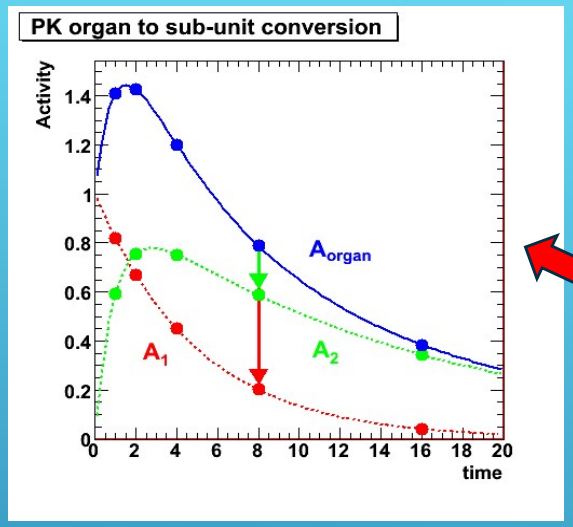
- size and parameters (range of values) for different compartments and cells
  - Tubule radius: (14 +/- 4) μm
  - Lumen radius: (4 +/- 2) μm
  - Glomerulus radius: (65 +/- 20) μm
- fractions of occupancy
  - Proximal tubule f_i: 81%, 53% (Proximal tubule cells f_i: 66%, 43%)
  - Glomerulus f_i: 2.3%, 1.5%

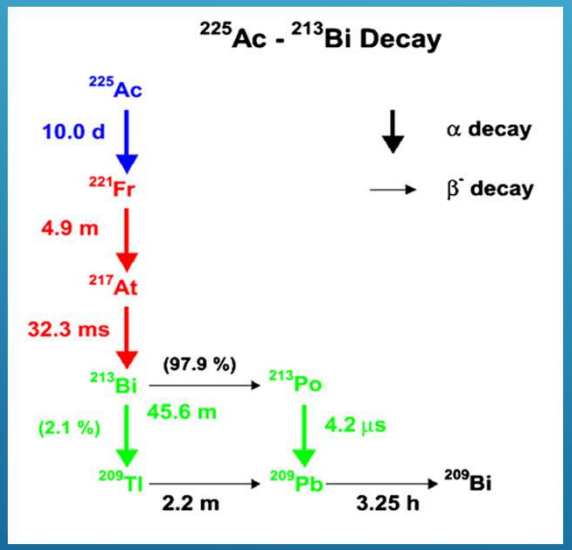




MACRO TO MICRO CONVERSION

- BUT! Cannot measure activity distribution directly with SPECT/CCT or PET/CT!!
- Measure (isotope) activity conc $a_j(t)$ in compartments AND whole organ
- Multiply by fraction of occupancy f_i to apportion fraction of activity g_i to compartments
- Account for daughters - Free ^{213}Bi, eg
- Human translation/scaling.
- **M2μ Is NOT specific to any scale or model, but tis the principle of apportionment and scaling from a sub-imaging scale to the visible scale**
- **Does not need to be done routinely. Once conversion factors are established, input will still be organ time ordered activity**





$$A_{organ} = g(SC) \cdot \tilde{A}_j$$

$$D_i = \sum_j S_{i \leftarrow j} \cdot \tilde{A}_j$$

Hobbs et al. Phys Med Biol '12

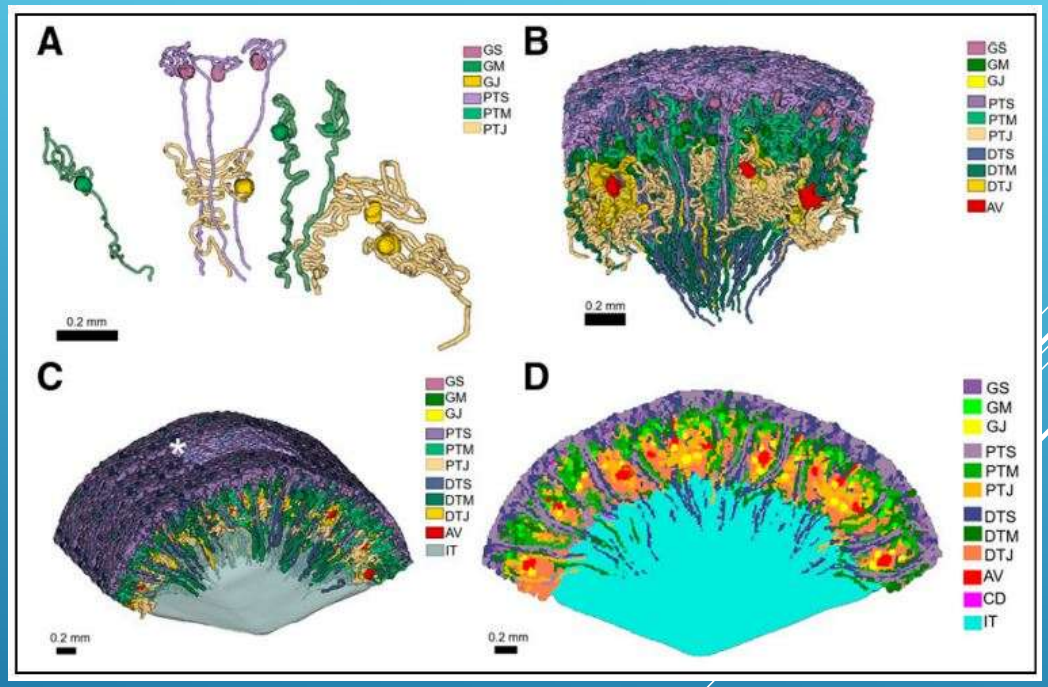
NEW PUBLICATION

A Computational Multi-nephron Model for Small-Scale Preclinical Renal Dosimetry in Radiopharmaceutical Therapy

Beautiful imaging data and anatomical model. Detailed, distinguishes between superficial [S], midcortical [M], and juxtamedullary [J] nephrons.

Large *S* value dependence on different nephron type "justifies" this approach, but ignores the reality that activity is rarely if ever measured throughout the entire compartment of proximal tubules.

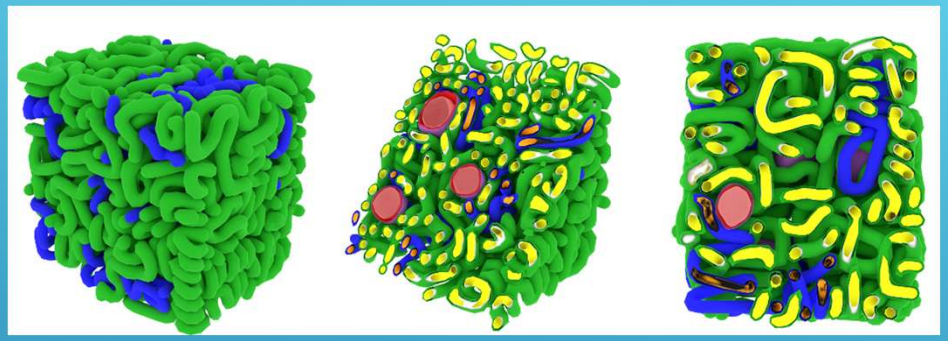
Differences are an artifact of the geometry of the tubules which are "never" a reflection of the activity distribution.



Andersson et al. JNM '25

HUMAN MODELS COMPACT SCALE FOR ALPHAS

- 1 mm^3
- Polygon mesh model of renal labyrinth
- S values do NOT agree with published values by a significant margin
- What is the right S value ?
- Several different scenarios, none of which may be applicable to the specific RPT that is studied



Bonnie President PhD Dissertation '24
U Florida

Both models have merit and can potential be quite useful, but need to reflect actual activity distributions within the different traditional anatomical compartments and be applied to the physiological compartments as applicable.

S VALUE PROBLEM: IS IT REALLY A MIRD METHOD ?

Which S values are the right ones.

Other models of complete single nephrons have been made with very different S values

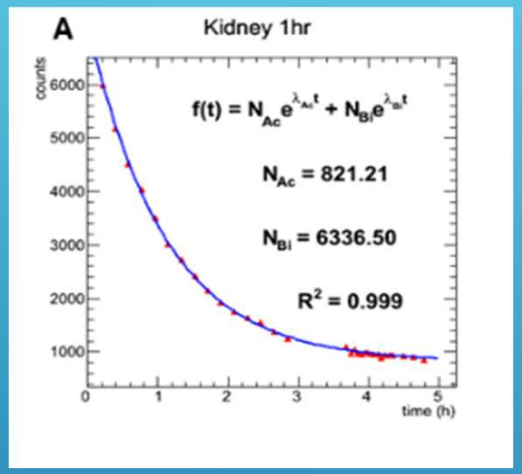
$$D_i = \sum_j S_{i \leftarrow j}\left(\tilde{A}_j\right) \cdot \tilde{A}_j$$

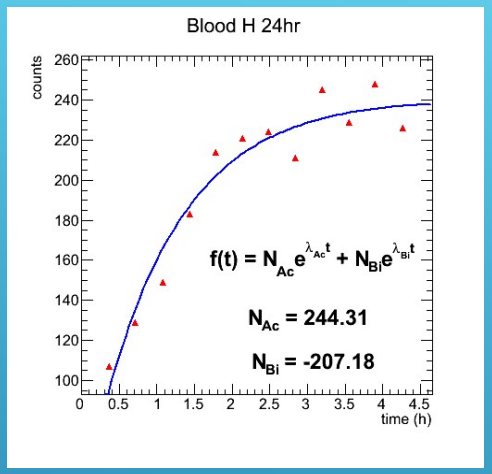
Becoming apparent that the approach is not as disjointed as the formula implies and is actually closer to voxelized approach of Monte Carlo simulations on realistic phantom

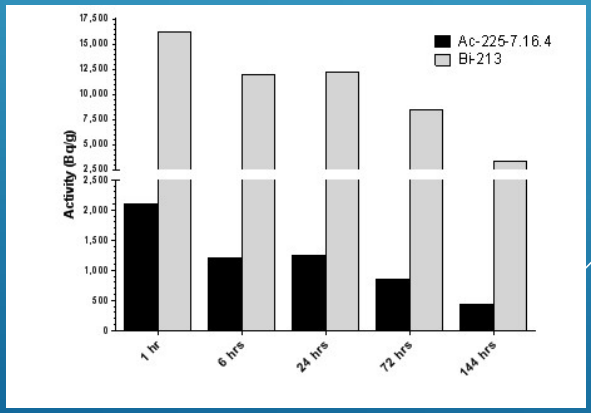
Regions of interest are more than just anatomically determined regions, but are defined by physiology as well. Ergo, if one really wants to speak in terms of S values, they are very specific to each RPT as they depend on the activity distributions

APPORTIONMENT: ORGAN ACTIVITY QUANTIFICATION

- Measure in γ – counter
- Only ^{213}Bi emits photons
- Fit to double exponential to quantify activities at time sacrifice
- Different RPTs have different source organs for ^{213}Bi – many have ^{225}Ac uptake (peptides, small molecules)

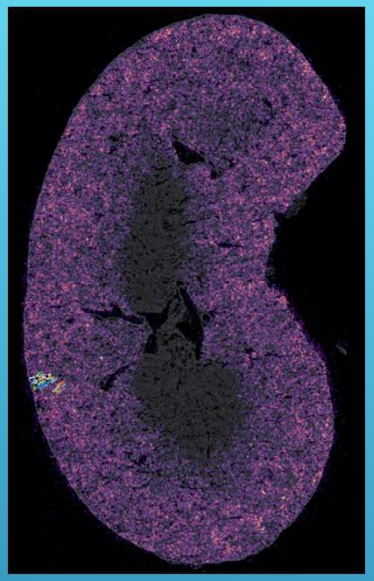


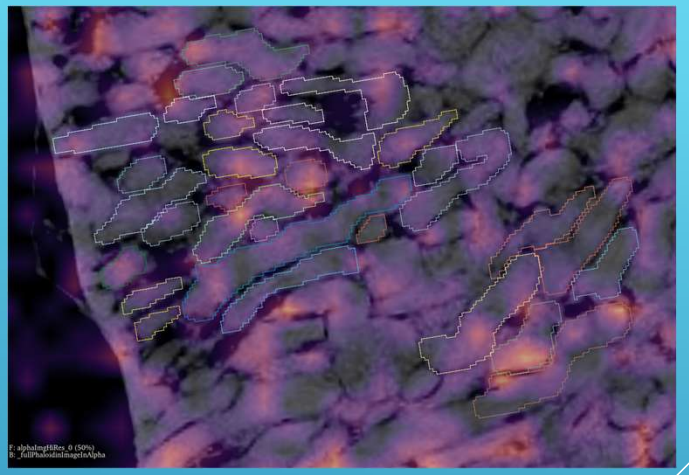


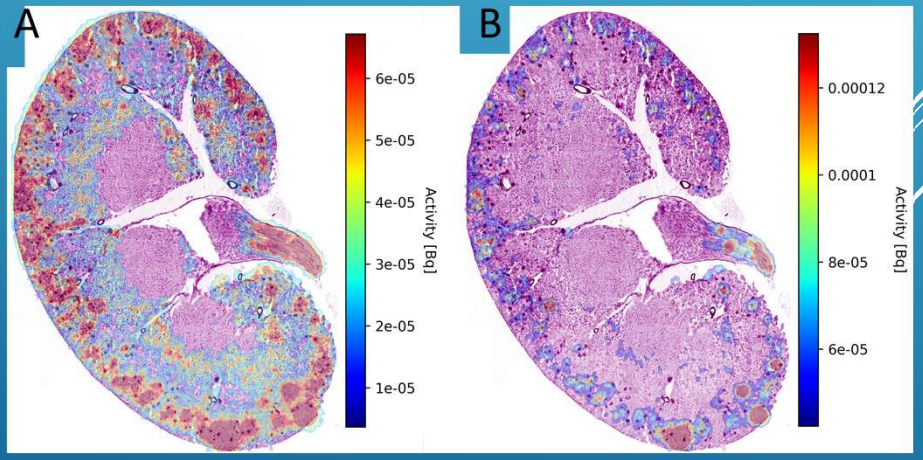


LOCALIZATION

- Registration between slices is an issue – resolved using same slice and refined registration techniques*
- Old data used consecutive slices, registration was painful and inadequate
- Multiple views and techniques to localize and quantify activity
- DISTRIBUTIONS within traditional compartments, try to characterize.







Sahota et al. Sci Rep '25

SPECIES-TO-SPECIES TRANSLATION

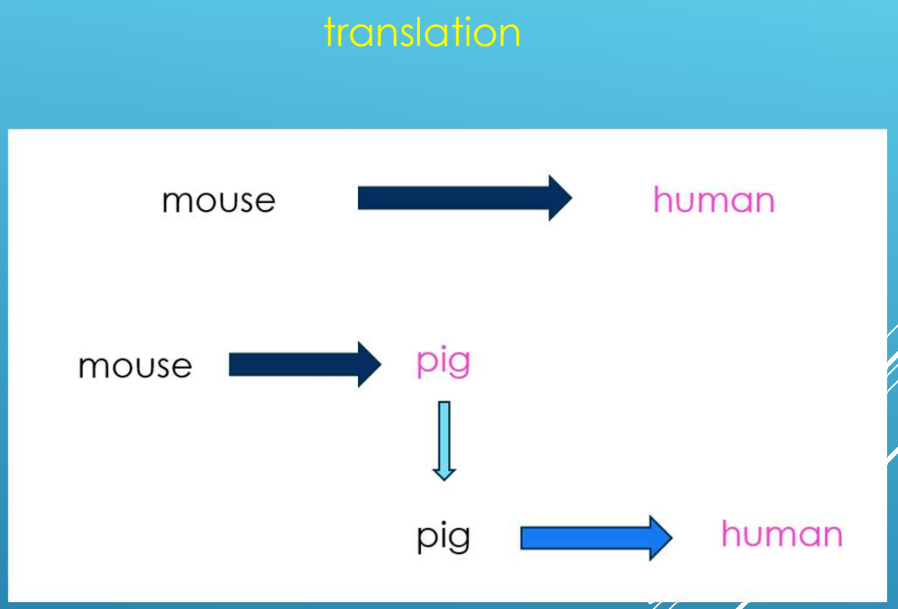
Species-to-species translation to be aided by introduction of pig model

Mice are not good models for several RPTs: - Ra223 where the epiphyseal plates are taking up most of the activity

- PSMA is not overexpressed in mouse models that we have seen

Pigs are closer to humans in size and anatomy/physiology.

Two different species allows for testing the species-to-species translation principles



CONCLUSIONS

Need more and better (in vivo) sRBEX data

Models for small scale dosimetry need to be married to measured data, translation to humans will benefit from larger animal models

Great progress in αRPT imaging in past few years, still need to translate to consistent, accurate quantification on commercial machines

Tumor dosimetry needs stochastic, probabilistic micro-dosimetry, may not correlate directly with response, given the non-uniform distribution and the unknown of immune response quantification.

AlphaRPT dosimetry still important for normal organ toxicity

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