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Dosimetry Needs and Methods for ^{225}Ac Systemic Radiation Therapy

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^{225}Ac Dosimetry Considerations

- Complexity of ^{225}Ac decay chain
- Stability of chelation and targeting scaffold
- Integrity of SRT following decay
  - Fate and toxicity of daughter isotopes released during decay
- Half-life of ^{225}Ac and daughters
- PK and tumor cell-uptake
  - nanogenerator

^{225}Ac Dosimetry Needs

Pre-clinical:

- Indirect methods to determine activities of administered ^{225}Ac and daughter isotopes
- Methods to determine activities in tissues (BD)
- Methods to determine micro-dosimetry

Clinical:

- Companion imaging tracer with comparable PK and BD
- Computational methods to estimate PK using companion imaging data
- Computational methods to estimate dosimetry of ^{225}Ac and daughters using companion imaging data

Moffitt ^{225}Ac Dosimetry Methods

Pre-clinical:

- Use of isomeric gamma spectra to calculate associated alpha emission activity of ^{225}Ac and daughters.
- Ex vivo BD time-course to calculate time-activity curves for use in calculating dosimetry via the MIRD schema.
- Multicompartment PK modeling using BD data.
- Alpha-camera acquisitions and IHC staining for correlating mechanism of cellular damage and cell-death with microdosimetry.
- Companion imaging tracer development.
  - Ga-67 SPECT (2.8 d $T_{1/2}$) and Ga-68 PET (20 min $T_{1/2}$)

Clinical:

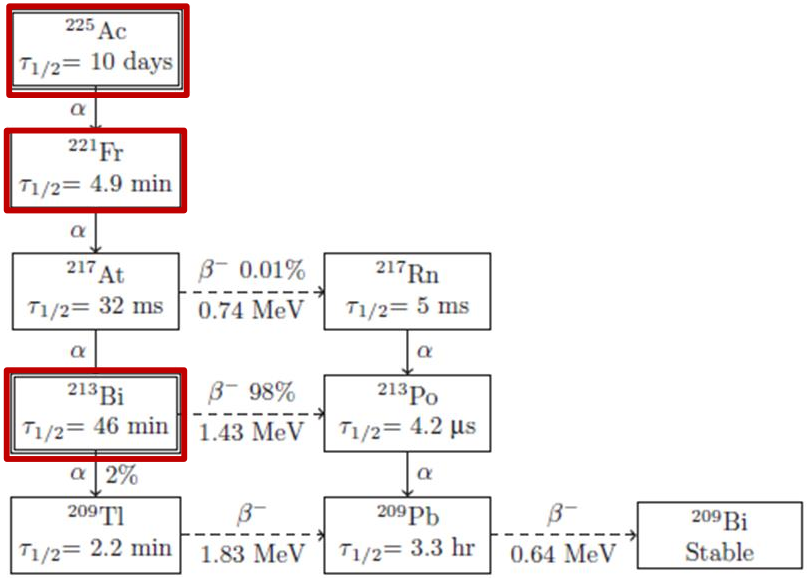
- Companion image-based multicompartment PK modeling.
- Personalized voxel-based dosimetry.

Determination of ^{225}Ac and daughter product α-emission activities

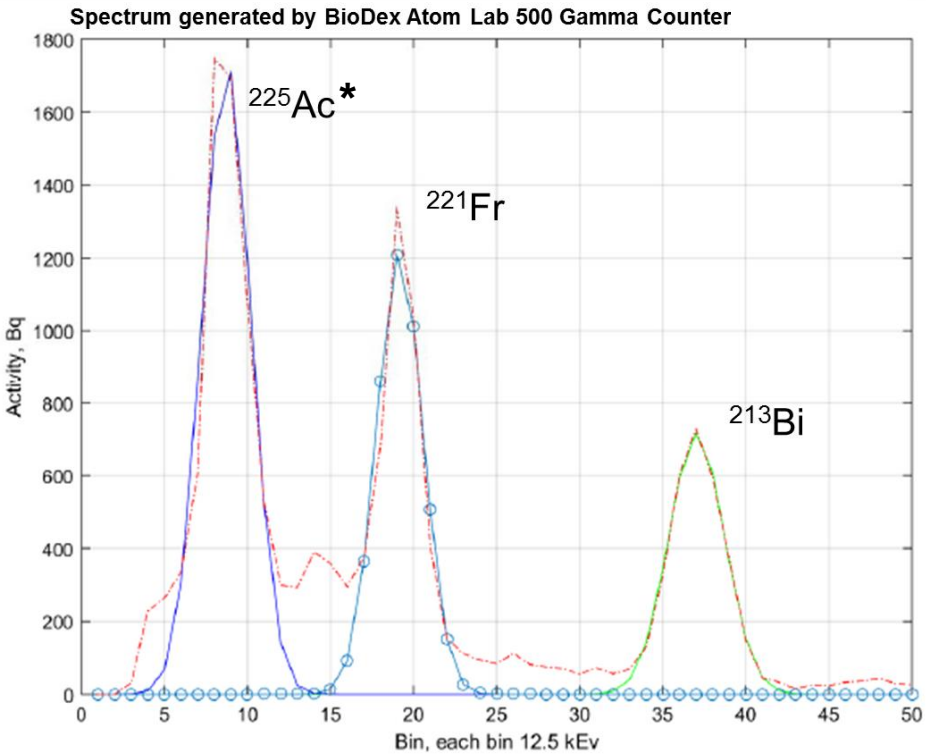
- Accurate measurement of activities in pre-clinical models is necessary for development of computational methods for estimation of clinical dosimetry.
- Few have instrumentation to directly measure α-emission activity.
  - ^{225}Ac and daughters in decay chain have associated γ-emissions.
  - Measure gamma spectra to calculate associated α-emission activities of ^{225}Ac and daughters.
- Dose calibrator measurements and gamma counters have different sensitivities
  - Monte Carlo simulations are used to determine the activity response relationships between the different instruments.

Gamma spectra for calculation of alpha activities

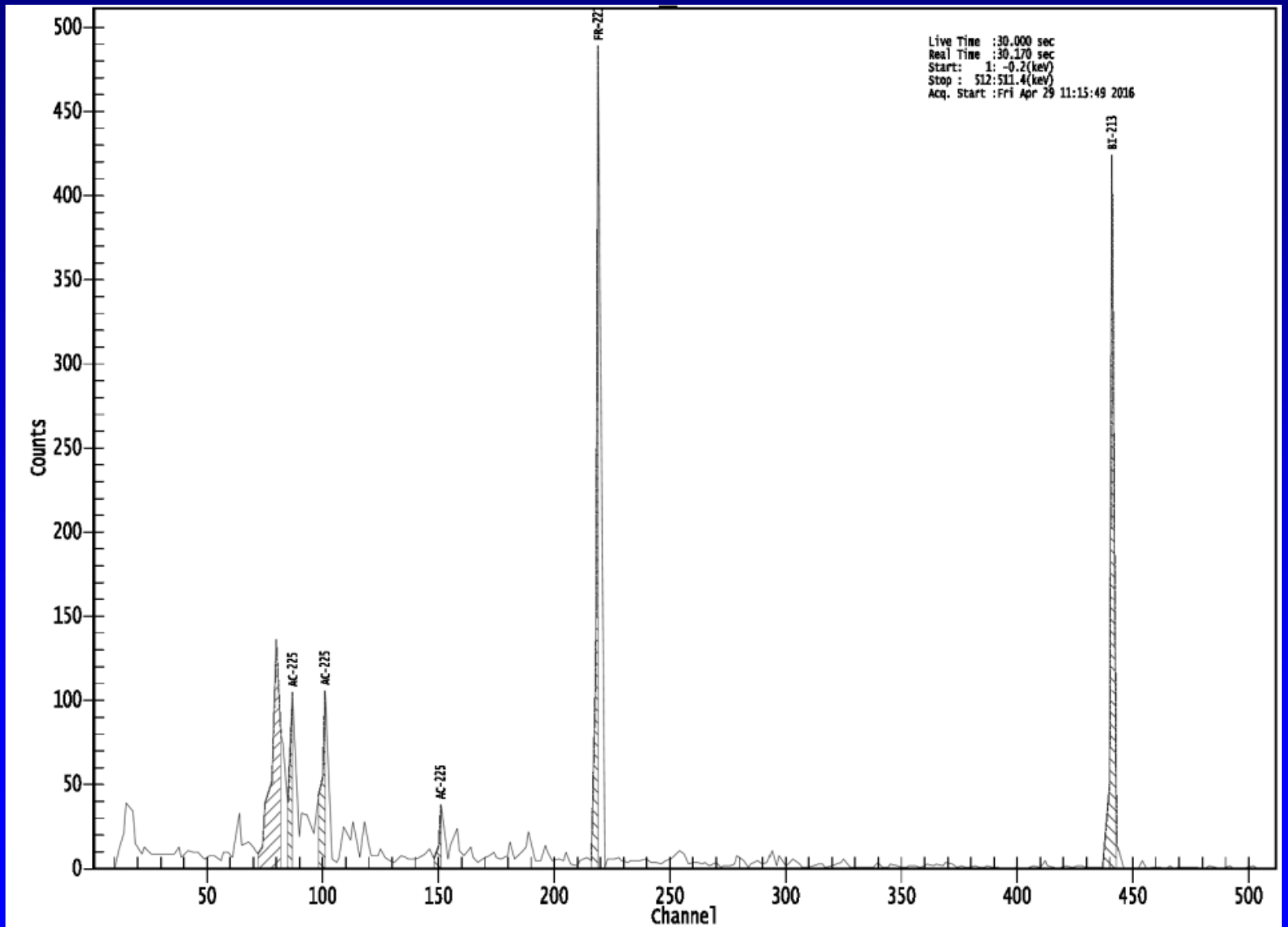
^{225}Ac decay chain



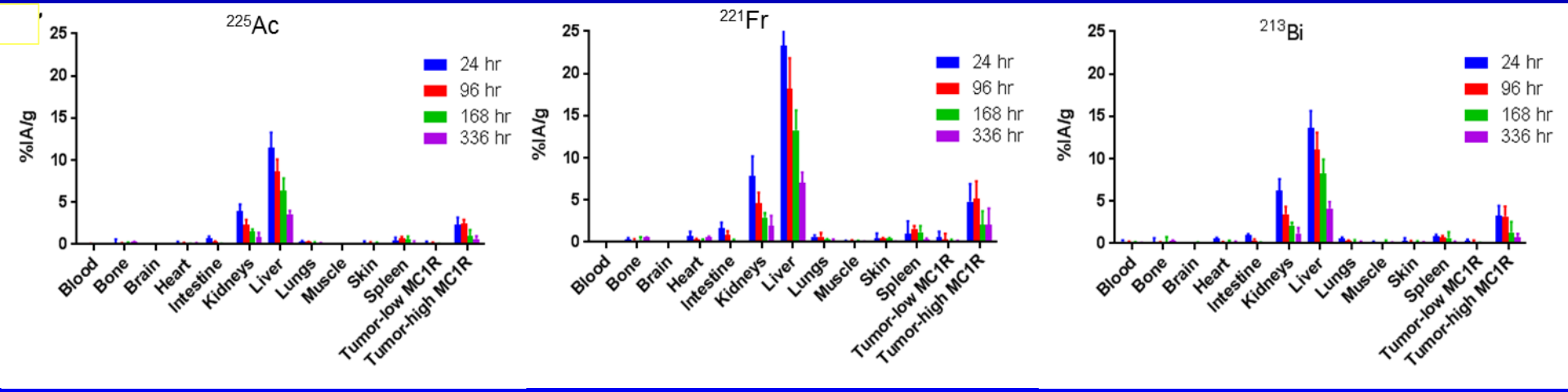
Gamma spectrum of ^{225}Ac and decay products in a tissue specimen using a NaI(Tl).



Canberra high resolution gamma spectrometer with HPGe detector (1.5 keV resolution)

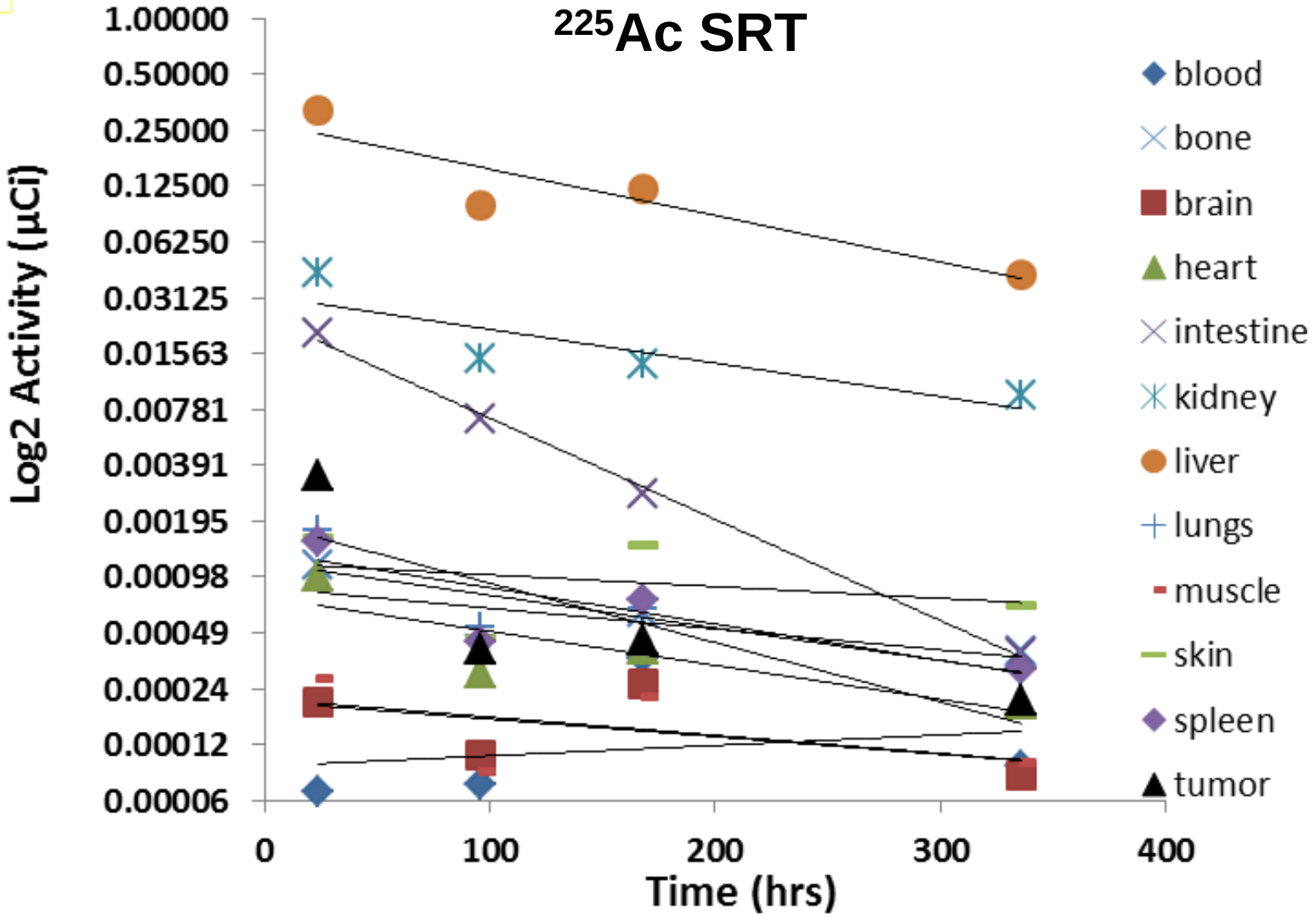


BD time course with calculated alpha activities for ^{225}Ac and daughter isotopes



Fitting calculated BD activities:

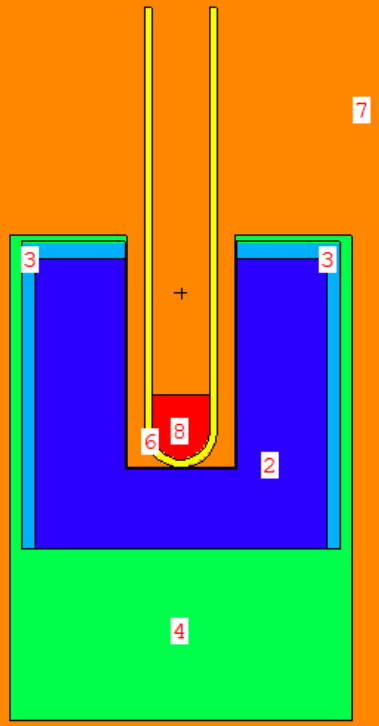
can be done for γ-emitting isotopes in decay chain



Dosimetry calculations per MIRD

^{225}Ac												
Parameter	Blood	Bone	Brain	Heart	Intestine	Kidney	Liver	Lung	Muscle	Skin	Spleen	Tumor
Initial activity/organ, A_o (µCi)	0.0001	0.0011	0.0002	0.0010	0.0199	0.0421	0.3164	0.0017	0.0003	0.0016	0.0015	0.0034
Decay rate constant, λ_{eff} (h^{-1})	0.0013	0.0030	0.0020	0.0040	0.0130	0.0040	0.0060	0.0040	0.0020	0.0010	0.0040	0.0070
Decay half-life, T_{eff} (days)	22.2163	9.6270	14.4406	7.2203	2.2216	7.2203	4.8135	7.2203	14.4406	28.8811	7.2203	4.1259
Accumulated activity/organ, Ã (µCi*h)	0.0170	0.2130	0.0451	0.1605	1.0991	6.8207	38.6351	0.2814	0.0606	0.4150	0.2428	0.3646
Absorbed dose/injected activity (Gy/µCi)	0.0026	0.1514	0.0101	0.0854	0.0443	1.1782	2.4734	0.1072	0.0275	0.0460	0.4000	0.1919
^{221}Fr												
Parameter	Blood	Bone	Brain	Heart	Intestine	Kidney	Liver	Lung	Muscle	Skin	Spleen	Tumor
Initial activity/organ, A_o (µCi)	0.0001	0.0005	0.0002	0.0005	0.0072	0.0167	0.1212	0.0013	0.0002	0.0010	0.0007	0.0022
Decay rate constant, λ_{eff} (h^{-1})	0.0018	0.0020	0.0020	0.0030	0.0090	0.0040	0.0050	0.0040	0.0020	0.0020	0.0010	0.0070
Decay half-life, T_{eff} (days)	16.0451	14.4406	14.4406	9.6270	3.2090	7.2203	5.7762	7.2203	14.4406	14.4406	28.8811	4.1259
Accumulated activity/organ, Ã (µCi*h)	0.0223	0.1109	0.0352	0.0980	0.6035	2.6986	16.9752	0.2167	0.0424	0.2167	0.1819	0.2335
Absorbed dose/injected activity (Gy/µCi)	0.0100	0.2340	0.0234	0.1548	0.0722	1.3837	3.2260	0.2449	0.0570	0.0713	0.8897	0.3649
^{217}At												
Parameter	Blood	Bone	Brain	Heart	Intestine	Kidney	Liver	Lung	Muscle	Skin	Spleen	Tumor
Initial activity/organ, A_o (µCi)	0.0001	0.0005	0.0002	0.0005	0.0072	0.0167	0.1212	0.0013	0.0002	0.0010	0.0007	0.0022
Decay rate constant, λ_{eff} (h^{-1})	0.0018	0.0020	0.0020	0.0030	0.0090	0.0040	0.0050	0.0040	0.0020	0.0020	0.0010	0.0070
Decay half-life, T_{eff} (days)	16.0451	14.4406	14.4406	9.6270	3.2090	7.2203	5.7762	7.2203	14.4406	14.4406	28.8811	4.1259
Accumulated activity/organ, Ã (µCi*h)	0.0223	0.1109	0.0352	0.0980	0.6035	2.6986	16.9752	0.2167	0.0424	0.2167	0.1819	0.2335
Absorbed dose/injected activity (Gy/µCi)	0.0114	0.2674	0.0267	0.1769	0.0825	1.5813	3.6868	0.2799	0.0652	0.0815	1.0168	0.4170
^{213}Bi												
Parameter	Blood	Bone	Brain	Heart	Intestine	Kidney	Liver	Lung	Muscle	Skin	Spleen	Tumor
Initial activity/organ, A_o (µCi)	0.0000	0.0003	0.0001	0.0002	0.0044	0.0115	0.0793	0.0004	0.0000	0.0005	0.0003	0.0008
Decay rate constant, λ_{eff} (h^{-1})	0.0008	0.0020	0.0006	0.0030	0.0100	0.0040	0.0060	0.0050	0.0020	0.0050	0.0030	0.0050
Decay half-life, T_{eff} (days)	36.1014	14.4406	48.1352	9.6270	2.8881	7.2203	4.8135	5.7762	14.4406	5.7762	9.6270	5.7762
Accumulated activity/organ, Ã (µCi*h)	0.0090	0.0595	0.0155	0.0315	0.3293	1.8596	9.6798	0.0497	0.0078	0.0682	0.0502	0.1083
Absorbed dose/injected activity (Gy/µCi)	0.0001	0.0030	0.0002	0.0012	0.0009	0.0228	0.0439	0.0013	0.0003	0.0005	0.0059	0.0040
^{213}Po												
Parameter	Blood	Bone	Brain	Heart	Intestine	Kidney	Liver	Lung	Muscle	Skin	Spleen	Tumor
Initial activity/organ, A_o (µCi)	0.0000	0.0003	0.0001	0.0002	0.0044	0.0115	0.0793	0.0004	0.0000	0.0005	0.0003	0.0008
Decay rate constant, λ_{eff} (h^{-1})	0.0008	0.0020	0.0006	0.0030	0.0100	0.0040	0.0060	0.0050	0.0020	0.0050	0.0030	0.0050
Decay half-life, T_{eff} (days)	36.1014	14.4406	48.1352	9.6270	2.8881	7.2203	4.8135	5.7762	14.4406	5.7762	9.6270	5.7762
Accumulated activity/organ, Ã (µCi*h)	0.0090	0.0595	0.0155	0.0315	0.3293	1.8596	9.6798	0.0497	0.0078	0.0682	0.0502	0.1083
Absorbed dose/injected activity (Gy/µCi)	0.0054	0.1661	0.0136	0.0658	0.0521	1.2607	2.4323	0.0743	0.0139	0.0297	0.3244	0.2238
Total absorbed dose/injected Activity (Gy/µCi)	Blood	Bone	Brain	Heart	Intestine	Kidney	Liver	Lung	Muscle	Skin	Spleen	Tumor
	0.0295	0.8220	0.0740	0.4841	0.2520	5.4267	11.8624	0.7076	0.1639	0.2290	2.6366	1.2016

Dose calibrator vs. NaI(Tl) gamma counter:
Monte Carlo simulations are used to determine the activity response relationship

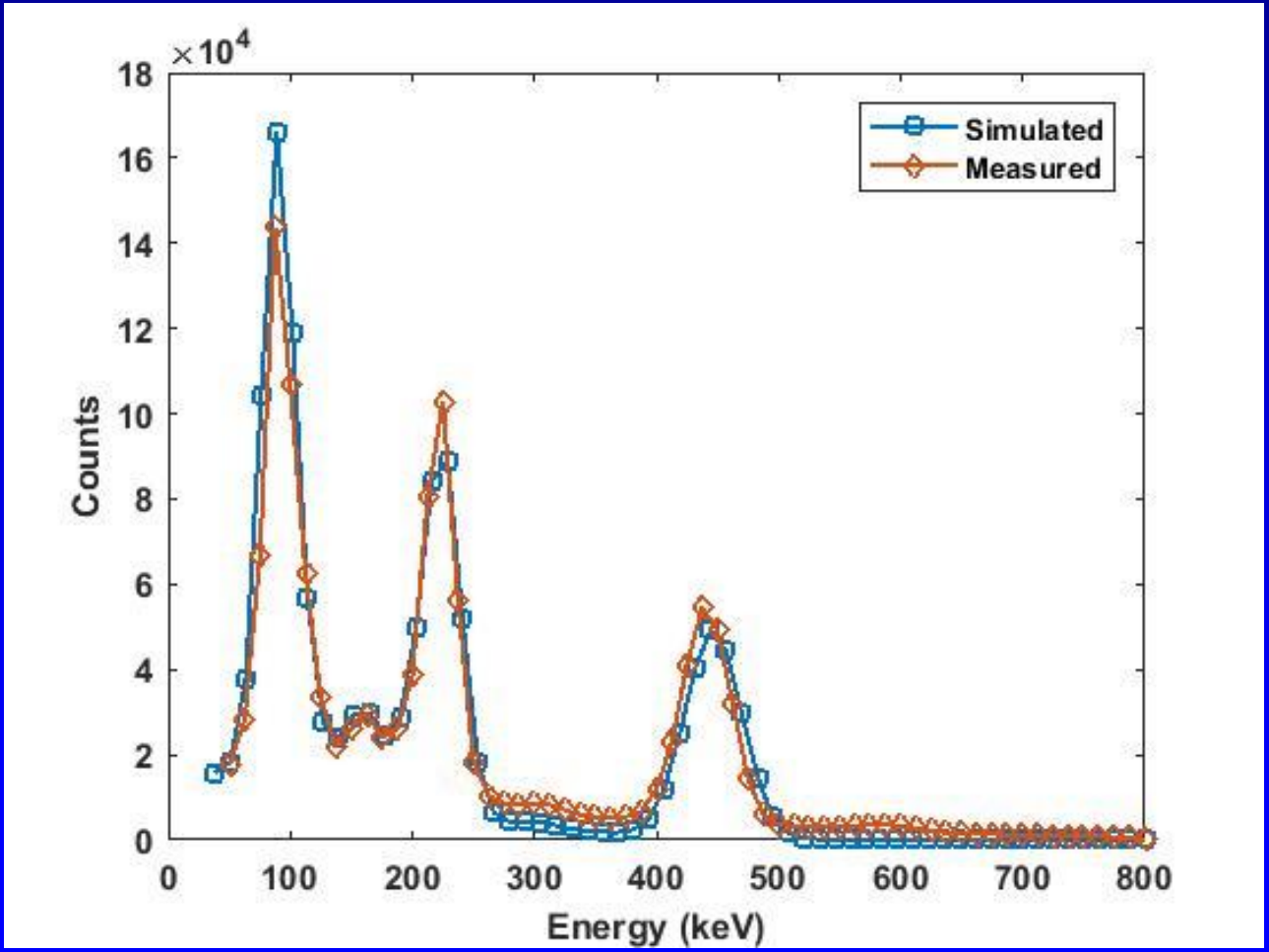


Geometry of the Monte Carlo model.

- Cell 2: NaI;
- Cell 3: MgO;
- Cell 4: Al;
- Cell 6: Polyethylene;
- Cell 7: Air;
- Cell 8: H20 with ^{225}Ac, ^{221}Fr, ^{213}Bi source distributions.

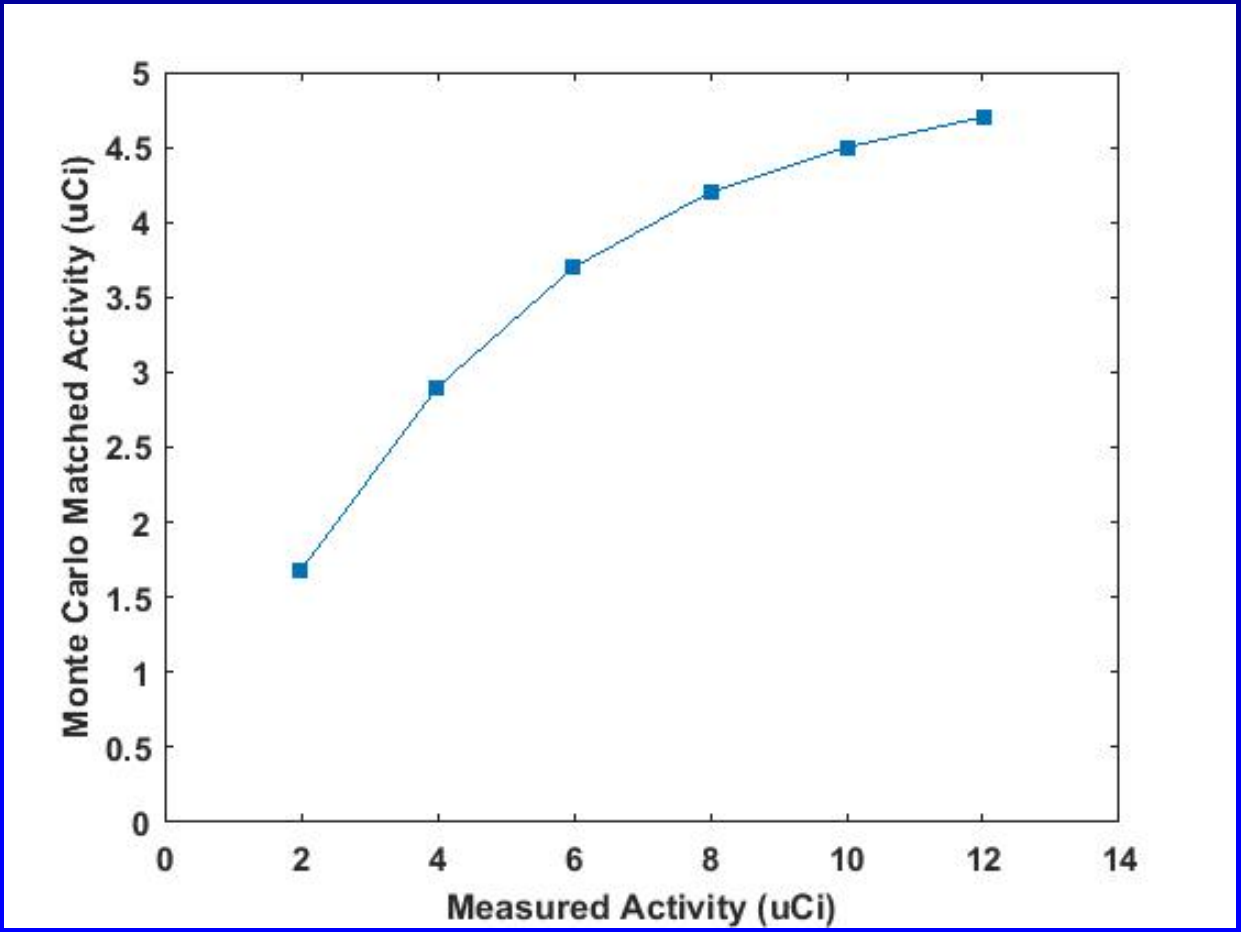
See Tichacek poster

MCNP simulated 2.9 µCi ^{225}Ac gamma spectrum matched the 4.0 µCi spectrum measured with NaI(Tl) detector



See Tichacek poster

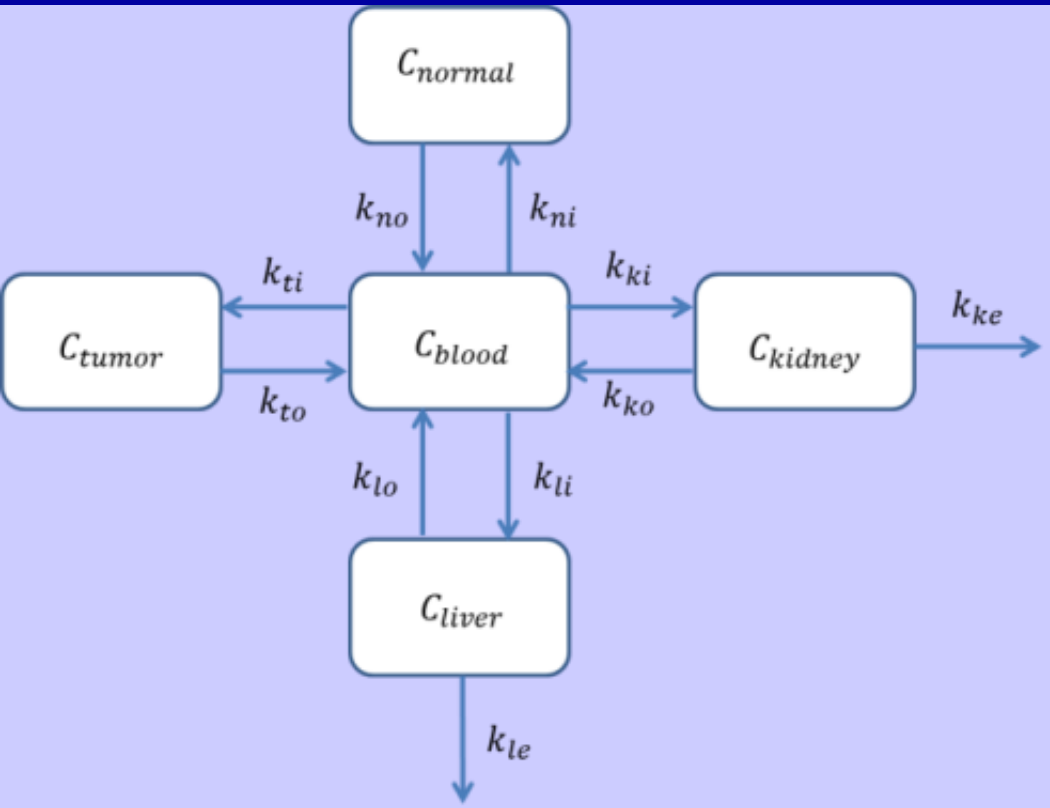
Activity response relationship between dose calibrator reading and Monte Carlo matched spectra activity



See Tichacek poster

Multi-compartmental PK model

Schematic



System of ODE's that represent the change in compartmental radioactive concentrations

$$\frac{dC_{tumor}}{dt} = k_{ti}C_{blood} - k_{to}C_{tumor}$$

$$\frac{dC_{normal}}{dt} = k_{ni}C_{blood} - k_{no}C_{normal}$$

$$\frac{dC_{kidney}}{dt} = k_{ki}C_{blood} - k_{ko}C_{kidney} - k_{ke}C_{kidney}$$

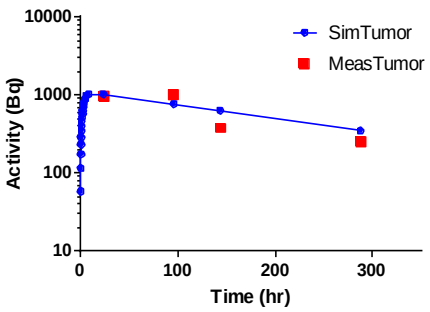
$$\frac{dC_{liver}}{dt} = k_{li}C_{blood} - k_{lo}C_{liver} - k_{le}C_{liver}$$

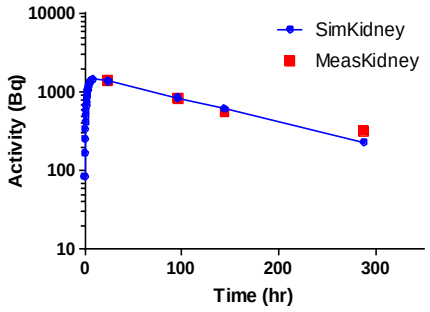
$$\frac{dC_{blood}}{dt} = -(k_{ti}C_{blood} - k_{to}C_{tumor}) - (k_{ni}C_{blood} - k_{no}C_{normal}) - (k_{ki}C_{blood} - k_{ko}C_{kidney} - k_{ke}C_{kidney}) - (k_{li}C_{blood} - k_{lo}C_{liver} - k_{le}C_{liver})$$

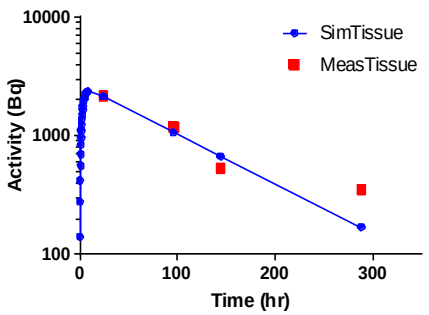
See Tichacek poster

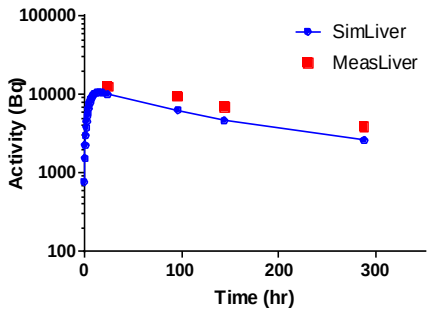
Multi-compartmental PK model fitting and rate estimation using calculated alpha activities

Fitting the model solutions to the experimental BD data with optimization by the genetic algorithm.









Calculated PK transfer and elimination rates for two ^{225}Ac SRTs. All values are [1/hour].

Compound	kti	kto	kni	kno	kki	kko	kke	kli	klo	kle
225Ac-DOTA-Ahx-MC1RL	0.0031	0.0008	0.0130	0.0025	0.0034	0.0035	0.0008	0.1193	0.0227	0.0002
225Ac DOTA-di-D-Glu-MC1RL	0.0026	0.0003	0.0010	0.0057	0.0015	0.0071	0.0002	0.0022	0.0081	0.0001

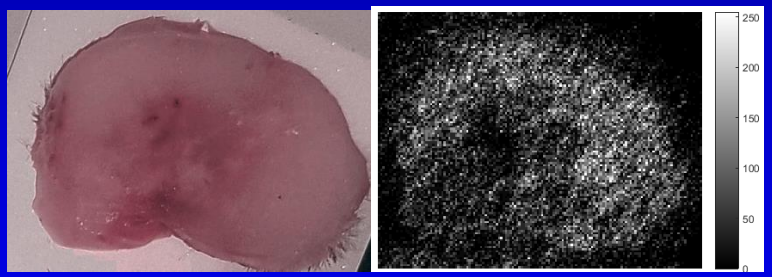
See Tichacek poster

Microdosimetry: Alpha-camera acquisitions and IHC staining

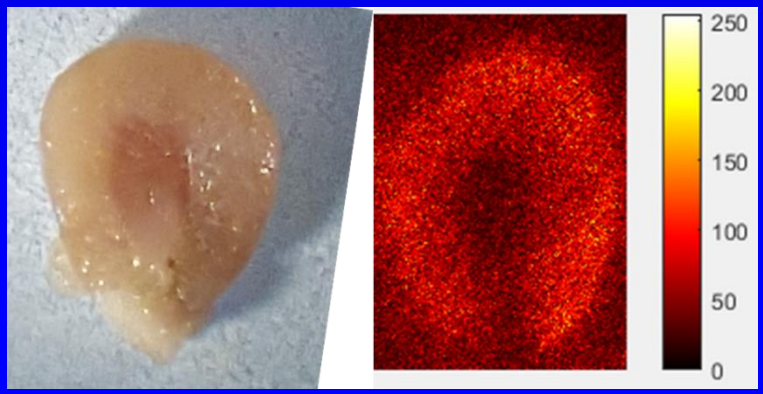
- Ex vivo alpha-camera images of tissue sections can determine regional heterogeneity of activity distribution.
- IHC of the same section to register activity-related damage and mechanism of cell death.

Ionizing-radiation Quantum Imaging Detector (iQID, Center for Gamma Ray Imaging, The University of Arizona)

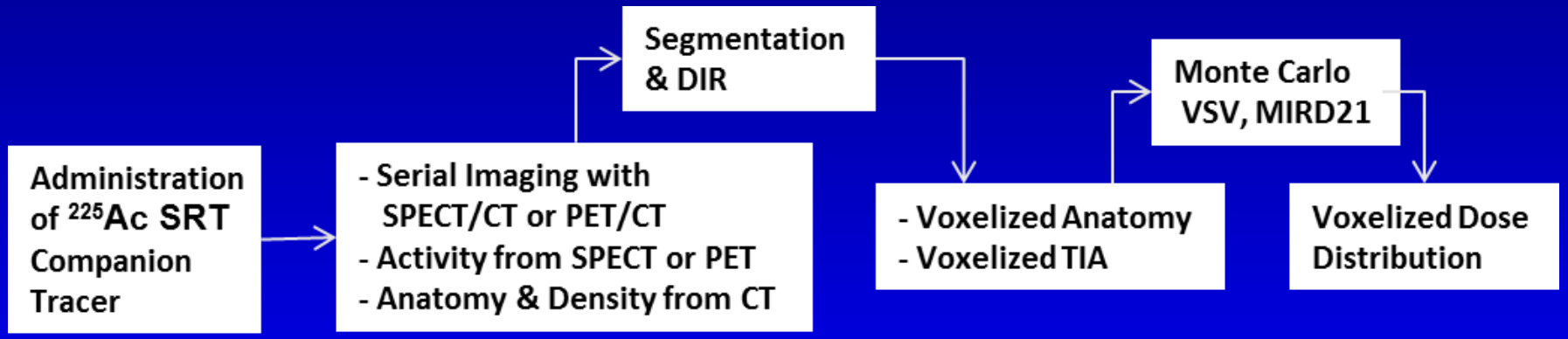
tumor



kidney



Voxel-based dosimetry for clinical translation of ^{225}Ac SRT



General procedure for voxel-based dosimetry.

SPECT=Single Photon Emission CT; CT=Computed Tomograpy; PET=Positron Emission Tomography; DIR=Deformable Image Registration; TIA=Time-Integrated Activity; VSV=Voxel S Values; MIRD=Medical Internal Radiation Dose methodology.

See Moros abstract

Conclusions: Considerations and Needs

- Complexity and timing of the ^{225}Ac decay in relationship to radiopharmaceutical stability, uptake and clearance.
  - Decay product toxicity in clearance organs.
  - Small molecule and peptide agents with rapid uptake and clearance – the nanogenerator approach.
- Companion imaging tracers with BD comparable to the SRT are needed for clinical ^{225}Ac voxel-based dosimetry for clinical risk assessment.

Conclusions: Methods

- Clinical companion imaging data can be used for multi-compartmental modeling to estimate PK.
- Accurate ^{225}Ac and daughter isotope activity determinations are necessary to enable the use of pre-clinical studies to inform computational models for clinical risk assessment.
  - Gamma spectra for calculation of isotope-specific alpha activities.
  - Activity response relationship for instrumentation used in measurement of low activities used for pre-clinical measurements.
- Microdosimetry methods are needed to understand regional dosing and mechanisms of damage and cell death.

Moffitt ^{225}Ac Dosimetry Team

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Christopher Tichacek, MS, Medical Physics Graduate Student, University of South Florida

Posters and abstracts:

Tichacek CJ, Budzevich MM, Morse DL, Moros EG. A Monte Carlo Method for Determining the Response Relationship Between Two Commonly Used Detectors to Indirectly Measure Alpha Particle Activity.

Tichacek CJ, Budzevich MM, Wadas TJ, McLaughlin ML, Moros EG, Morse DL. Multicompartment Pharmacokinetics Modeling of ^{225}Ac-based Targeted Alpha Particle Therapy (TAPT).

Moros EG, Tichacek CJ, Budzevich MM, Morse DL. Voxel-based Radiation Dosimetry for Clinical Translation of Targeted Alpha Particle Therapy.