Early-Phase Development of Therapeutic Radiopharmaceuticals and Theranostics

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Oncology Therapy Development Workshop: Pivotal Steps and Avoiding Pitfalls for Start-Ups
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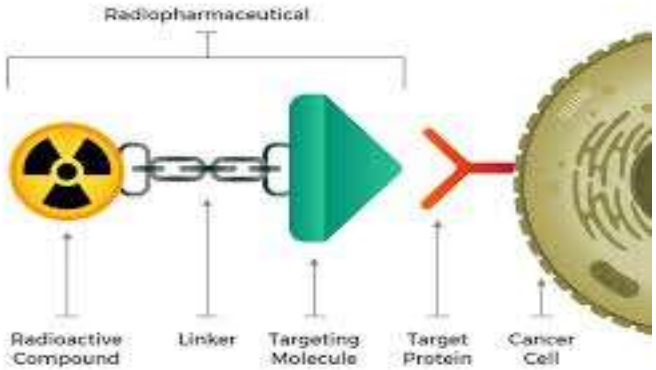
Objectives

- Provide Information to Assist Sponsors in the Design of Early-Phase Studies for the Development of Therapeutic Radiopharmaceuticals
- Provide Overview of Dosimetry Regulations and Methods for Diagnostic and Therapeutic Radiopharmaceuticals

Content

- Introduction
  - Radiopharmaceuticals (RPs)
- Design of Early-Phase Studies to Support FIH trials with Therapeutic RPs
  - Dosimetry Regulation: CFR Title 21 (21CFR312.23), and FDA Guidances
- Dosimetry for Diagnostic and Therapeutic RPs
  - The Medical Internal Radiation Dose (MIRD) Formalism
  - Dosimetry for Radiopharmaceutical Therapy (RPT)

Radiopharmaceuticals (RPs)



NCI – Cancer.gov

- Combination of a **Radionuclide** with a **Biologically Active Pharmacophore**

- Building on **natural affinity** (ex. I-131 for thyroid cancer, Ra-223 dichloride for metastatic bone cancer)

<u>Diagnostic RPs</u>:

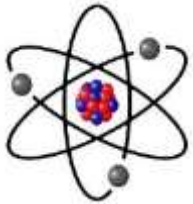
- Sub-pharmacological doses,
- Trace a particular physiological or pathological process in the body.

<u>Therapeutic RPs:</u>

- Deliver radiation **directly** and **specifically** to cancer cells.

Attributes of Radiopharmaceuticals

Combination of a Radionuclide with a Biologically Active Pharmacophore



- Determines imaging (permitting external detection) and/or therapeutic properties
- Can also confer the desired localization properties (for ex. radio-iodine)

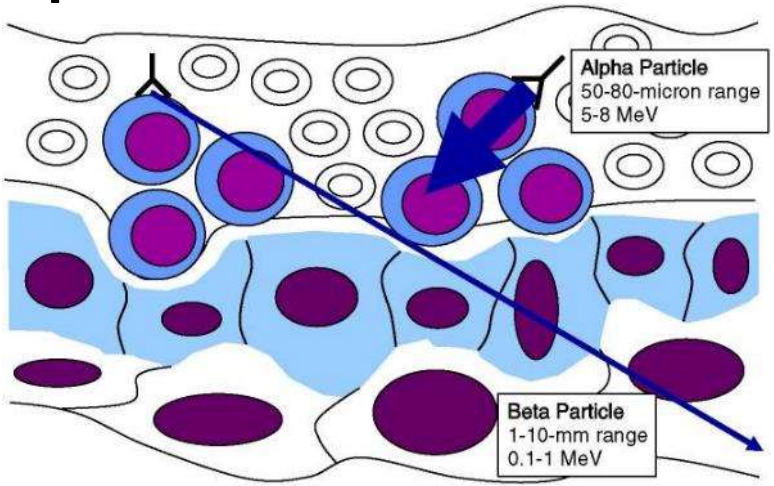
- Overall chemical structure determines biological properties
- Acts as a carrier
- Determines localization and bio-distribution

Emission Types in RPT

β-Particles
- Elementary particle
- Sparsely ionizing
- Path length ~0.8-10 mm
- 0.2 keV/µm (**LOW LET**)
- 10^3 to 10^4 tracks to kill cell
- DNA damage is repaired

α-Particles
- He nucleus
- Densely ionizing
- Kinetic energy: 4-9 MeV
- Path length: 50-100 µm
- ~60-240 keV/µm (**HIGH LET**)
- 2-3 tracks kill cell
- Irreparable DNA damage

Photons (γ-rays)
- Used for imaging

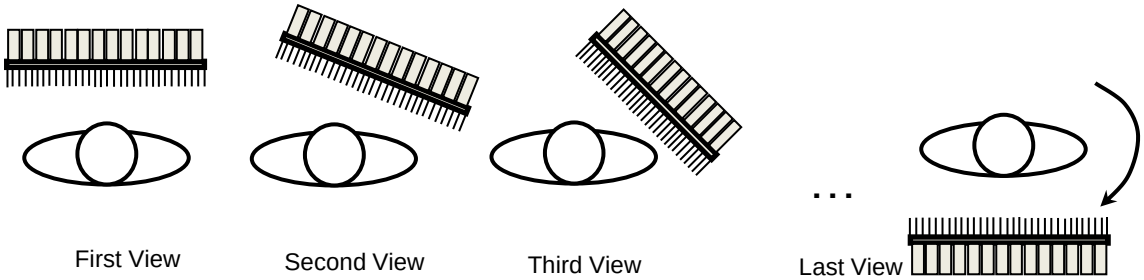


Milenic et al. Nature Rev. Drug. Disc. 2004, 3, 488

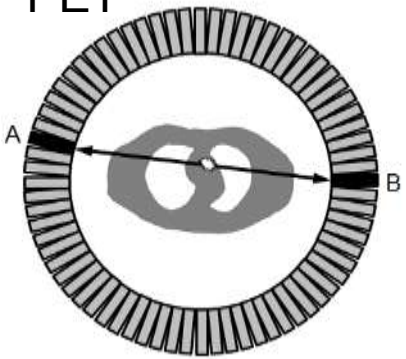
Therapeutic Radionuclides	
Beta Emitters	**Alpha Emitters**
Examples: **I-131, Y-90, Sm-153, Lu-177, Sr-89**	Examples: **Ra-223, Ac-225, Th-227**

Imaging Radionuclides

SPECT



PET



Planar Imaging, SPECT	PET
Examples: **Tc-99m, I-123**	Examples: **F-18, C-11, Ga-68**

- **Physical Properties of the Radionuclide: Half-life** (observational time window)
- **Imaging Modality Specifications:**
  - **Collimators** and **Efficiency** (% of detected/emitted photons)
  - **Sensitivity** (ability to detect and record the emitted events)
  - **Quantification** (very important for dosimetry)

Dosimetry Regulations

- For radioactive drugs, 21 CFR 312.23(a)(10)(ii) requires that IND submissions include "*sufficient data from animal or human studies to allow a reasonable calculation of radiation absorbed-dose to the whole-body and critical organs upon administration to a human subject*".
- Phase-1 studies must include studies which will obtain sufficient data for dosimetry calculations.
- For FIH studies, IND submissions include absorbed dose (AD) estimates for humans that are often extrapolated from pre-clinical (animal) biodistribution data.

Radiation Dosimetry

- Why do we need to perform radiation dosimetry?
  - A measure to predict potential toxicity/efficacy and risk associated with exposure to radiation
- Internal Dosimetry
  - Ingestion or internal administration of radioactivity
- Absorbed Dose
  - Amount of energy absorbed/mass in target organ/tissue
  - Most closely related to the biological effect
- Optimal dosing for RPT
  - Achieve good tumor response w/o causing normal organ toxicity

Early-Phase Development Studies

FDA Guidance (Oncology Therapeutic RPs: Nonclinical Studies and Labeling Recommendations - August 2019):

- Proof-of-concept studies prior to a FIH study
- Preliminary characterization of the mechanism of action (in-vitro studies for target-binding and anti-tumor activity and animal studies)
  - Species selection for biodistribution and toxicology studies
- Pharmacology studies to determine MTD in animals.

Pre-clinical Biodistribution Studies

FDA Guidance (Oncology Therapeutic RPs: Nonclinical Studies and Labeling Recommendations - August 2019):

- Single-dose administration and single-animal species (both M & F)
- Evaluate radioactivity in organs over time
  - **Sufficient Duration of Sampling** - Multi-exponential time-activity curve may necessitate many sampling time-points and increase # of animals (refer to MIRD Pamphlet 16)
- Collect PK parameters
- Consider all daughter decays and their half-lives when designing the animal study
- Modeling can be used to fit the time-activity curve, should be described in the IND application
- Incorporate aspects of the planned clinical biod. and dosimetry study (to ensure consistency)

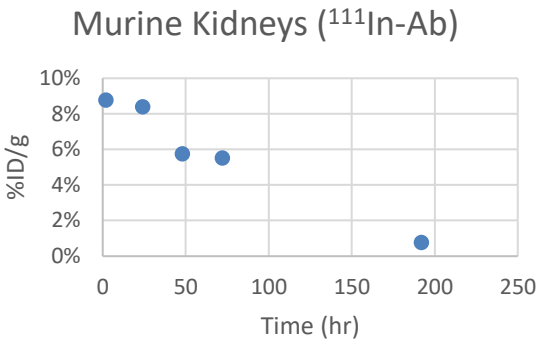
Pre-clinical Biodistribution Studies

FDA Guidance (Oncology Therapeutic RPs: Nonclinical Studies and Labeling Recommendations - August 2019):

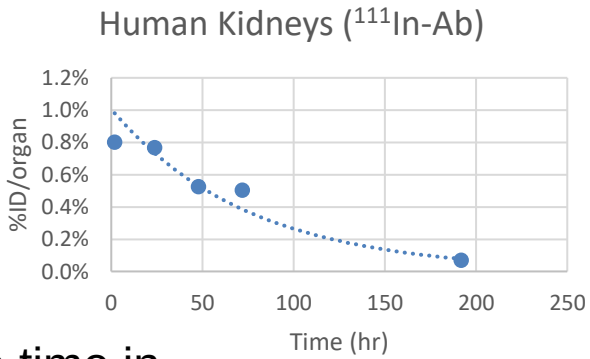
- Selection of organs to assess biodistribution
  - Bone-marrow, organs of excretion (kidneys, liver) and all organs w/ potential uptake specific to the particular RP
  - Both M&F organs unless indication is gender-specific
- Collect excretion data
- Larger animals (ex. monkeys, dogs) are done by imaging - smaller # of animals may be sufficient, 3M & 3F)
  - Characterize time-activity data on selected source organs
- Smaller animals (ex. mice, rats) are done by animal sacrifice - sufficient # of animals/time-point
  - Radioactivity is counted (ex. gamma counter) and used to characterize biod.

Animal to Human Conversion Relative Organ-Mass Extrapolation

$$[\%ID/organ]_H = [\%ID/g]_A \cdot TBM_A \cdot \frac{OM_H}{TBM_H}$$



Assumption: *the metabolism of RPs is similar between animals and humans and varies only as a function of organ mass.*



Pre-clinical Studies for RPT

- Project rough normal organ dosimetry to help guide clinical trial design – may underpredict actual residence time in human organs
- Could be used to identify unexpected high uptake
- Method of extrapolation (animal-to-human) should be described in the IND submission

Medical Internal Radiation Dose (MIRD) "Absorbed Fraction" Methodology

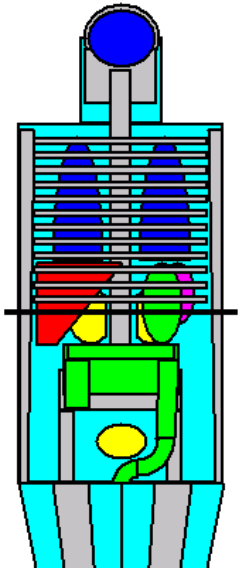
***$\tilde{A}(r_S)$*:** Number of decays in ROI

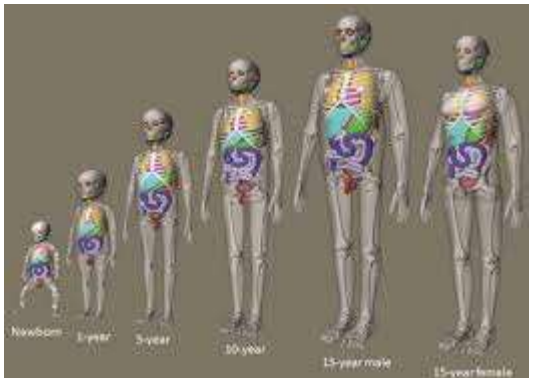
$$D(r_T) = \sum_{r_S} \tilde{A}(r_S) \cdot S(r_T \leftarrow r_S)$$

$D_t = \tilde{A}_{s1} \cdot S(t \leftarrow s1) + \tilde{A}_{s2} \cdot S(t \leftarrow s2) + \ldots.$

S-value: Pre-tabulated energy transfer coefficients:

- properties of the radionuclide
- organ anatomy
- organ mass





Digital anthropomorphic phantoms of varying size and anatomy, Uni. of Florida

The MIRD *S*-value schema (MIRD Pamphlet 21)

Bolch, W. E., et al (2009). MIRD pamphlet no. 21: a generalized schema for radiopharmaceutical dosimetry—standardization of nomenclature. *JNM*, *50*(3), 477-484.

www.fda.gov

Clinical Dosimetry Studies

FDA Guidance (Oncology Therapeutic RPs: Nonclinical Studies and Labeling Recommendations - August 2019): "When there is experience with the radionuclide or the ligand components of the RP being developed, the nonclinical program can be abbreviated as needed, and the FIH dose can be based on clinical data, as appropriate."

- **Small patient cohort,** both M & F
- **Number and distribution of imaging time-points (**MIRD Pamphlet #16**)**
  - Not-fixed (traditionally 3-5 imaging time-points – depends of PK)
  - Rapidly clearing activity: More frequent and early sampling
  - Slowly clearing activity: Fewer and widely dispersed samples
  - Refer to relevant quantitative data for similar RPs obtained in animal or human studies

MIRD Method - Radiation Dosimetry Based on Direct Measurements in Humans

1. Serial quantitative imaging
2. Co-registration across time
3. ROI (organ, tumor) segmentation
4. Model fitting and integration of the time-activity curve

$$\tilde{A} = \int_0^\infty A(t)dt$$

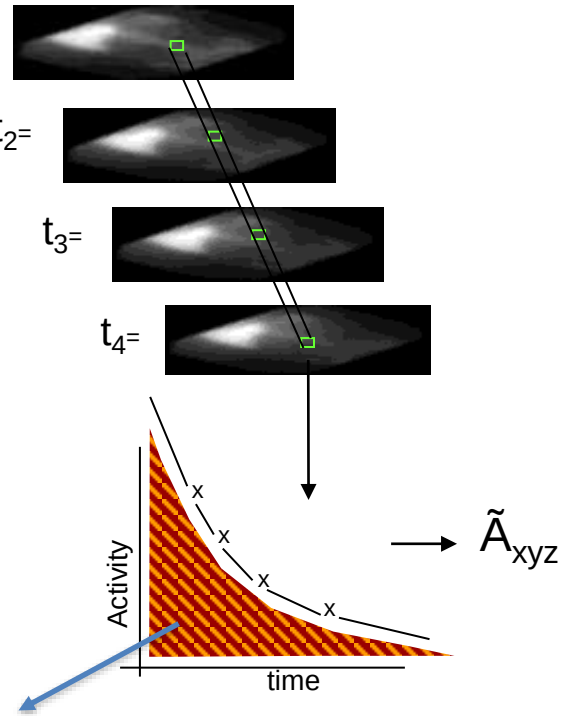
$$\tau = \frac{\tilde{A}}{A_0}$$

Residence time

5. Time-integrated activity to dose conversion

OLINDA/EXM Software Package, Stabin M.G. et al. *JNM*, 2005; 46: 1023-7

$$D(r_T) = \sum_{r_S} \tilde{A}(r_S) \cdot S(r_T \leftarrow r_S)$$



AUC = Number of decays

Dosimetry Method

MIRD Absorbed Fraction Method

- Dosimetry scheme for risk evaluation (relies on **reference geometry/anatomy** that is population averaged - no tumor dosimetry)
- **Activity-based** calculation using phantom derived S-values (organ masses should be modified based on available CT images)

Voxelwise Method

- **Patient-specific** dosimetry appropriate for RPT
- **Dose-rate based** calculation using Monte-Carlo and patient-specific anatomy
- Model **voxel-level** energy deposition for actual patient anatomy including tumors

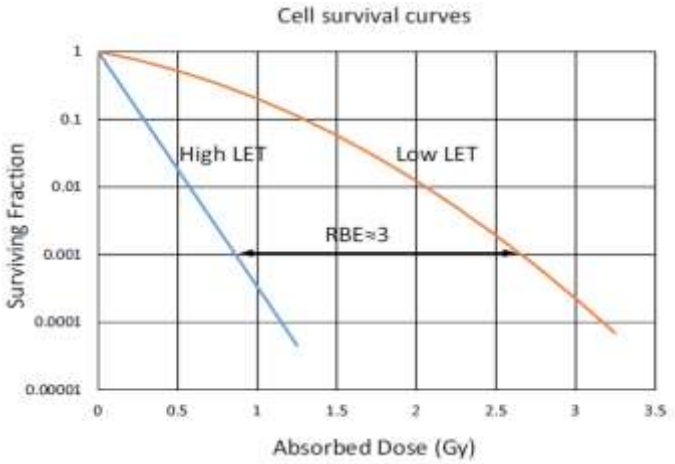
Table Dosimetry Platforms That Have Received 510(k) Clearance From the U.S. Food and Drug Administration, as of February 2020

Dosimetry Platform	510(k) Clearance Date	Dosimetry Method
OLINDA/EXM v1.0[27]	June, 2004	Absorbed Fraction
Hermes OLINDA/EXM v2.0	July, 2017	Absorbed Fraction
MIM SurePlan MRT	January, 2019	Voxelwise – Convolution
DOSIsoft PLANET Dose	March, 2019	Voxelwise – Convolution
Hermes Voxel Dosimetry	October, 2019	Voxelwise – Monte Carlo

Graves, S. A., & Hobbs, R. F. (2021, January). (Vol. 31, No. 1, pp. 37-44). WB Saunders

Dosimetry for α-Emitters

- AD estimates depend on PK fate of unstable daughters - consider half-life, biod. of daughters and radiosensitivity of organs
- Relative Biological Effectiveness (**RBE**), **RBE~3-7** but **depends on AD, biological endpoint, tissue type**



- Dosimetry method should account for both **organ-level** and **micro-scale** distributions (range is 50-100 µm)
  - **Macro-scale:** patient-imaging
  - **Micro-scale:** Combine whole-organ measurements with preclinical measurements – µ-scale biod./PK data in **sub-regions of critical organs**
  - Implement in the context of the MIRD methodology (MIRD Pamphlet 22)

$$D_{RBE}(r_T, r_D) = RBE_{\alpha} \cdot D_{\alpha}(r_T, rD) + RBE_{e} \cdot De\ (r_T, rD) + RBE_{ph} \cdot Dp_h\ (r_T, rD)$$

Sgouros, G., Hobbs, R., & Josefsson, A. (2018). Dosimetry and radiobiology of alpha-particle emitting radionuclides. *Current radiopharmaceuticals*, *11*(3), 209-214

Radiation-Induced Toxicity

- Long-term Toxicity Assessment to Support Marketing
  - Patients w/ long-life expectancy and expected late radiation AEs
  - Animal and human dosimetry AND publications on late radiation effects
  - Alternatively, an animal study can be conducted

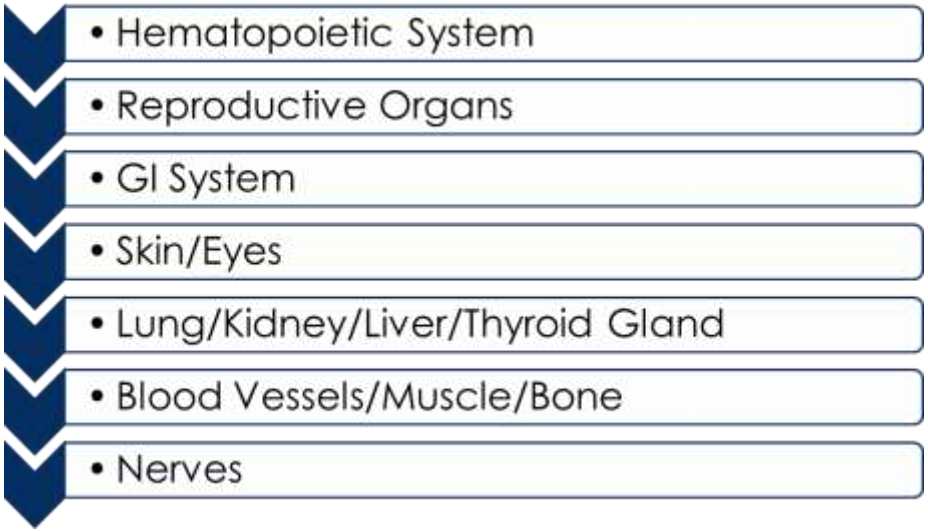
FDA Guidance: (Nonclinical Evaluation of Late Radiation Toxicity of Therapeutic Radiopharmaceuticals – November 2011):

- Estimated human organ-dosimetry & knowledge of organ-specific radiation-induced toxicities
- α and β radiation cause DNA damage and are inherently genotoxic and carcinogenic (communicate risks in product labeling)

Dose Selection for FIH Studies

FDA Guidance (Oncology Therapeutic RPs: Nonclinical Studies and Labeling Recommendations - August 2019):

- Administered activity (AA) should be adjusted based on tolerated radiation doses in human organs (using thresholds from EBRT as a starting point)
  - QUANTEC: Marks LB, *Int J Radiat Oncol Biol Phys*. 2010
  - Emami et al. 1991, Emami 2013, Stewart et al. 2012



- Cell-differentiation in tissue and radio-sensitivity
- Radio-sensitivity and clinical significance (i.e. lens of eye, spinal-cord)

Summary

- Non-clinical dosimetry studies extrapolated to humans can be used as a 1st approximation for radiation absorbed doses in human organs to select a starting human dose.
- Human dosimetry studies provide a clinically relevant estimate.
- Dosimetry for RPT has its roots in the formalism established by the MIRD Committee of SNMMI.
- **CFR Title 21 Regulation**: Nonclinical and clinical cohort dosimetry required for early-phase studies
- **Additional Considerations**: Patient-specific, voxelized and tumor dosimetry
- Early and frequent interaction with the FDA is recommended

Questions?

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