Dosimetric Effects of Weight-Based Activity of Pluvicto Using a PBPK Model

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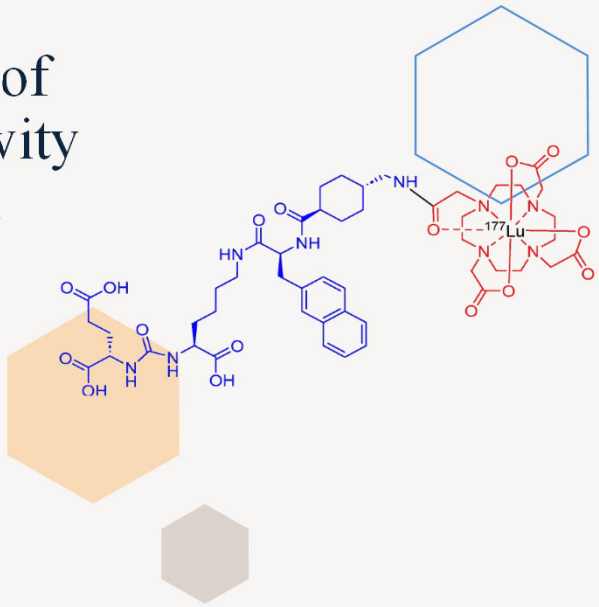


1

Agenda

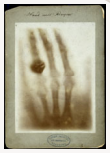
- What is a Radioligand?
- Pluvicto for mCRPC
- Pluvicto Dosimetry
- PBPK Modeling
- Next Steps

2

Short History of Radiation in Medicine

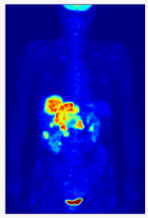
1895

William Roentgen Discovers X-Rays



1936

John Lawrence first uses Nuclear Medicine in Humans



1940

Use of Uptake of Radioactive Iodine to Treat Thyroid Cancer Reported

Early 1960s

Radioligands used to attempt to identify the estrogen receptor

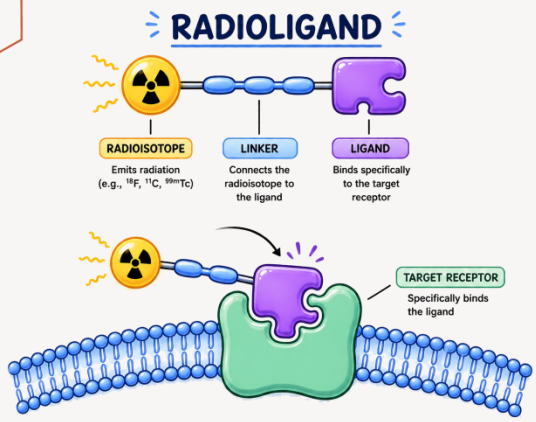
1973

PET Camera for Human Use

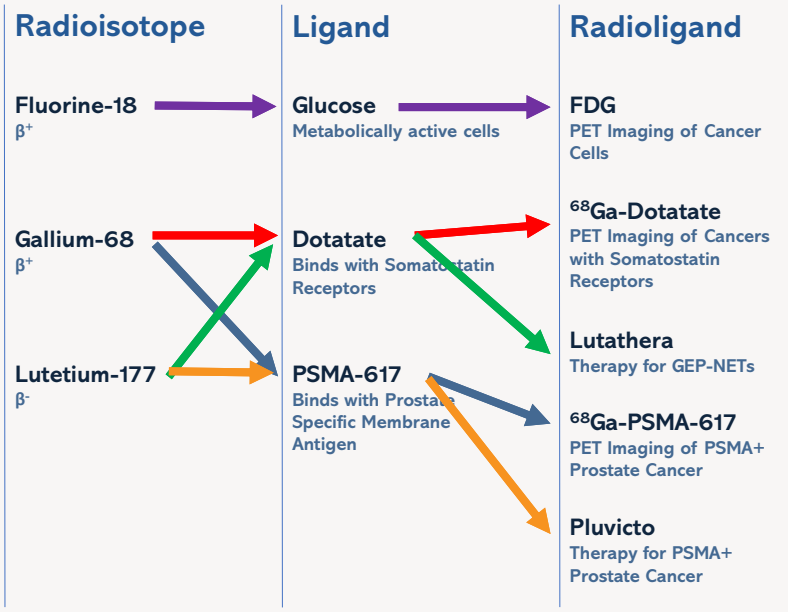
What is a Radioligand?

A Radioligand is a combination of:

- Radioisotope
  - Radioactive source
  - Alpha (α), Beta (β^- or β^+) or Gamma (γ)
- Ligand
  - Binds the Radioligand to the cancer cell
- Linker/Chelator (as needed) – Used to bind Radioisotope to Ligand



Some Radioligands



5

The Magic of Radioligands

Imagine a heat-seeking missile for cancer:

Travels through the body

Finds the cancer wherever its located and eliminates it

Low to no collateral damage to surrounding healthy tissue

But, just like at Disney, the Magic comes with a Cost

6

Radioligand Limitations

- **Production, Transportation and Storage Concerns**
  Short half-life improves performance and safety, but limits availability of radioisotopes
- **Damage to surrounding non-cancerous tissues**
  Use Alpha or Lower Energy (Shorter Range)
- **Image Resolution Decreased at Higher Energies**

7

Radioligand Limitations

- **Absorption of Radioligands by Tumor is Not 100% Efficient**
  FDG: Brain, Bladder Uptake often Exceeds Tumor
  Pluvicto: Kidney, Colon, Salivary Glands > 10% Dose to Tumor; Lacrimal Glands nearly 50% Tumor Dose
- **May lead to Adverse Reactions**
  Potential toxicities include myelosuppression, xerostomia, renal injury, and reproductive effects.

8

Radioligand Dosing Goal

Need to use enough dose for Tumor Control,

But not too much that other organs are negatively impacted

Patient Dosimetry is Critical

9

Pluvicto

- **Lutetium (^{177}Lu) vipivotide tetraxetan**
- **Beta$^-$ emitter Lu-177 combined with PSMA-617**
- **Half-Life of 6.64 days (biological half-life of ~41.6 hours)**
- **Also emits γ rays (at 112.9 and 208.4 keV) – SPECT imaging**

10

Pluvicto

- **Product of Novartis**
  Lutathera
  ^{68}Ga-PSMA-617
- **Phase III VISION trial completed in 2021**
- **followed by FDA "Breakthrough therapy" designation and later FDA approval in March 2022**
- **and EU approval in December 2022**

11

Pluvicto

- **Indicated for adult males w/ Prostate-Specific Membrane Antigen (PSMA)-positive Metastatic Castration-Resistant Prostate Cancer (mCRPC)**
- **Prior treatment with androgen receptor pathway inhibitor and taxane-based chemotherapy and no longer responding**
  Prior Chemo no longer required as of 2025
- **Demonstrate PSMA expression through PET imaging (using ^{68}Ga-PSMA-11 or ^{68}Ga-PSMA-617):**
  Tumors and metastases are PSMA+ when radioligand uptake exceeds liver uptake
  All large tumors must be PSMA+

12

Pluvicto Delivery Workflow

1) PET Confirmation of PSMA+	2) Blood Count and Kidney Function Test	3) Pluvicto Administration	4) Post Treatment Dosimetry	5) Treatment Continuation
^{68}Ga-PSMA-617 & ^{177}Lu-PSMA-617 similar molecular geometries Baseline PSMA PET correlates well with subsequent Pluvicto uptake	Test results may delay start or continuation of treatment	Standard 7.4 GBq dose delivered intravenously Dose may be reduced by 20% due to test results or Adverse Reactions	Post-treatment SPECT/CT dosimetry may be performed when available	Repeat Steps 2 - 4 every 6 weeks for up to 6 total treatments Treatment may be delayed or discontinued due to Adverse Reactions

13

Radioligand Summary

RADIOLIGAND	DECAY MODES	ENERGY (mean/maximum)	RANGE (mean/maximum)	DOSING
FDG	β^+	249 keV / 634 keV	1 mm / 2.4 mm	**3.7 - 7.4 MBq/kg**
^{68}Ga-Dotatate	β^+	836 keV / 1.9 MeV	2.9 mm / 8.2 mm	**2 MBq/kg**
Lutathera	β^-	134 keV / 497 keV	0.67 mm / 2.2 mm	**7.4 GBq**
^{68}Ga-PSMA-617	β^+	836 keV / 1.9 MeV	2.3 mm / 8.2 mm	**111 – 259 MBq**
Pluvicto	β^- / γ	134 keV / 498keV	0.67 mm / 2.2 mm	**7.4 GBq**
Xofigo	α	5.78 MeV	57 µm	**55 kBq/kg**

14

Radioligand Dosing Goal

Need to use enough dose for Tumor Control,

But not too much that other organs are negatively impacted

Is Pluvicto's one-dose-fits-all best for ***ALL*** patients?

15

Is Pluvicto's 7.4 GBq Dose Best?

Maybe?

From Seifert et. al:

"There was no significant difference" in PSA change, mean estimated survival or organ toxicity between doses of 6 GBq and a 7.5 GBq[#]

and Calais et. al.:

"There was no difference in PSA RR [response rate] between administration of 6.0 and 7.4 GBq of 177Lu-PSMA"[^]

[#]Radioligand therapy using [177Lu]Lu-PSMA-617 in mCRPC: A pre-VISION single-center analysis (2022)

[^]Prospective phase 2 trial of PSMA-targeted molecular RadiothErapy with 177Lu-PSMA-617 for metastatic castration-reSISTant Prostate Cancer (RESIST-PC): efficacy results of the UCLA cohort (2021)

16

Is Pluvicto's 7.4 GBq Dose Best?

But Probably Not for Every Patient

as Calais et. al. also states:

"Results justify confirmation with real-world data analysis and further trials to refine and optimize the 177Lu-PSMA therapy administration scheme to improve tumor radiation dose delivery and efficacy."^

And numerous other studies clearly show that patient tumor and organ doses vary widely on the standard 7.4 GBq dose.

^Prospective phase 2 trial of PSMA-targeted molecular RadiothErapy with 177Lu-PSMA-617 for metastatic castration-reSISTant Prostate Cancer (RESIST-PC): efficacy results of the UCLA cohort (2021)

17

Radioligand Dosing Goal

In a perfect world, all patients would receive SPECT imaging to calculate tumor and organ absorption

Dose could be varied to maximize efficacy while remaining below organ toxicity levels

But in the real world, we need other options

18

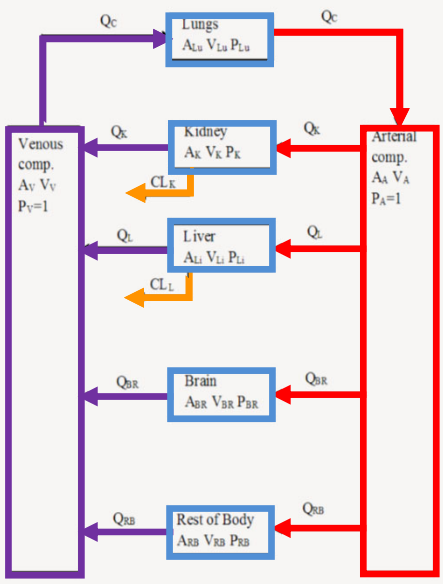
Physiologically Based Pharmacokinetic Modeling

A PBPK model is a computer simulation which calculates:

Absorption, Distribution, Metabolism, Excretion

of chemicals or drugs in living organisms, allowing for analysis of tumor absorption and organ toxicities

using compartments representing organs/tissues/blood and interconnected by the circulation of blood



19

PBPK Modeling

Why use PBPK?

- Demonstrate that modeling results accurately reflect the absorption of radiation in critical organs seen in patient imaging studies
- Show dosing variability can positively impact organ toxicity
- Potentially provide an alternative when SPECT is unavailable

20

PBPK Modeling

Methods

- **Initial proof-of-concept analysis using three representative patient phantoms spanning a clinically relevant weight range**

  Based on real patient data: height, weight, organ volumes

  Sizes: 75.6 kg, 92.6 kg, 108 kg

  92.6 kg phantom and standard (7.4 GBq) dose used as baseline

  Weight-, and BMI-scaled doses were defined

Phantom	Standard Dose	Weight Scaled	BMI Scaled
75.6 kg	7.4 GBq	6.04 GBq (81.6%)	6.38 GBq (86.2%)
92.6 kg	7.4 GBq	*	*
108 kg	7.4 GBq	8.63 GBq (116.6%)	8.39 GBq (113.4%)

21

PBPK Modeling

Methods

- **For each phantom and dose a model run was performed**

  Dose of Pluvicto administered at time, t=0

  Every 72s for 400 hours:
  Instantaneous Activities for 5 organ compartments: blood, salivary glands, kidney, liver and remaining tissues (Tumor dose currently excluded from analysis)

- **Calculated values for each organ compartment for each model run:**

  Absorbed Dose and Expected Absorbed Dose (Gy)
  Expected is baseline dose scaled for organ volume and Activity

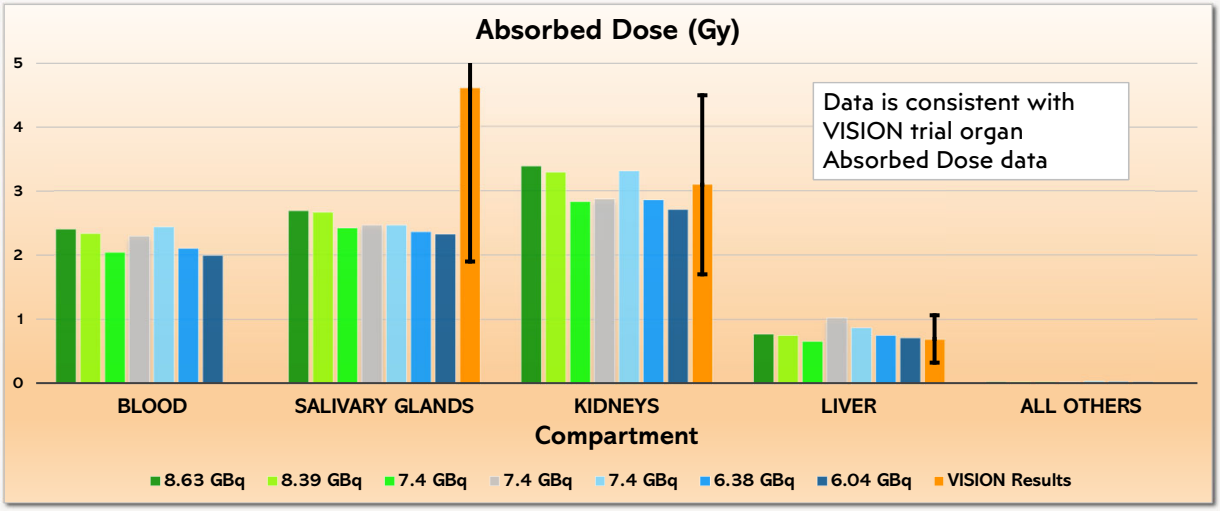
  Cumulative Absorbed Dose (ECD) – 6 Treatments

  Absorbed Dose per administered Activity (ADpA) (Gy/GBq)

  Normalized Absorbed Dose and ADpA (%, relative to the baseline)

22

Results



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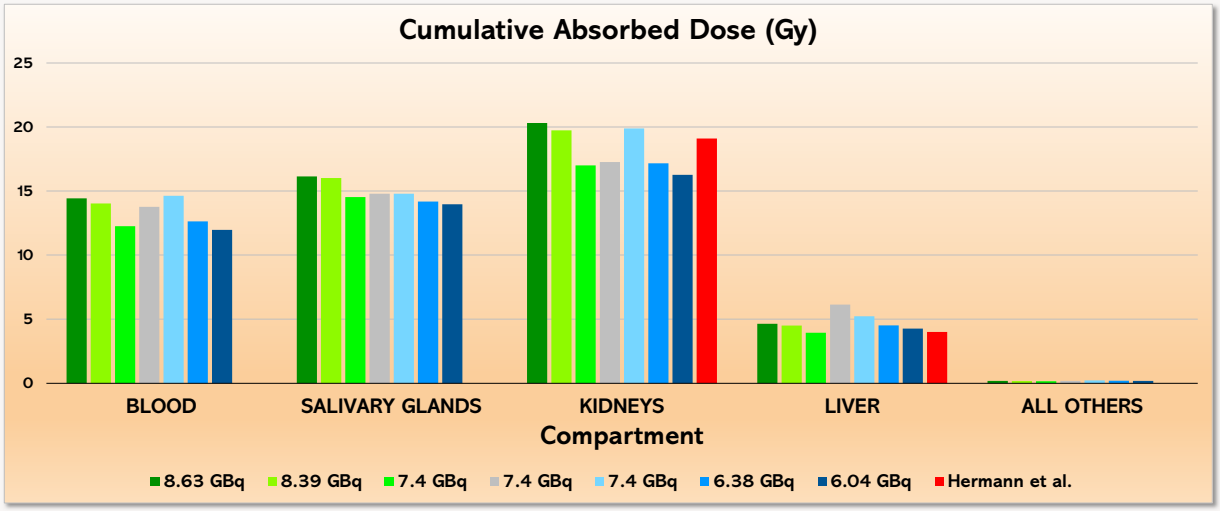
Results



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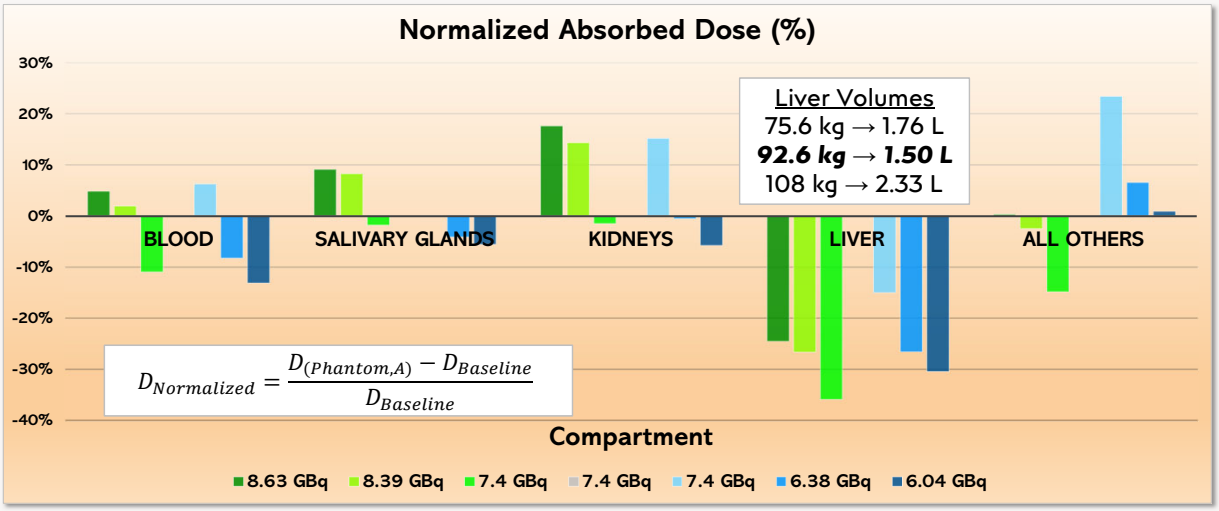
Results



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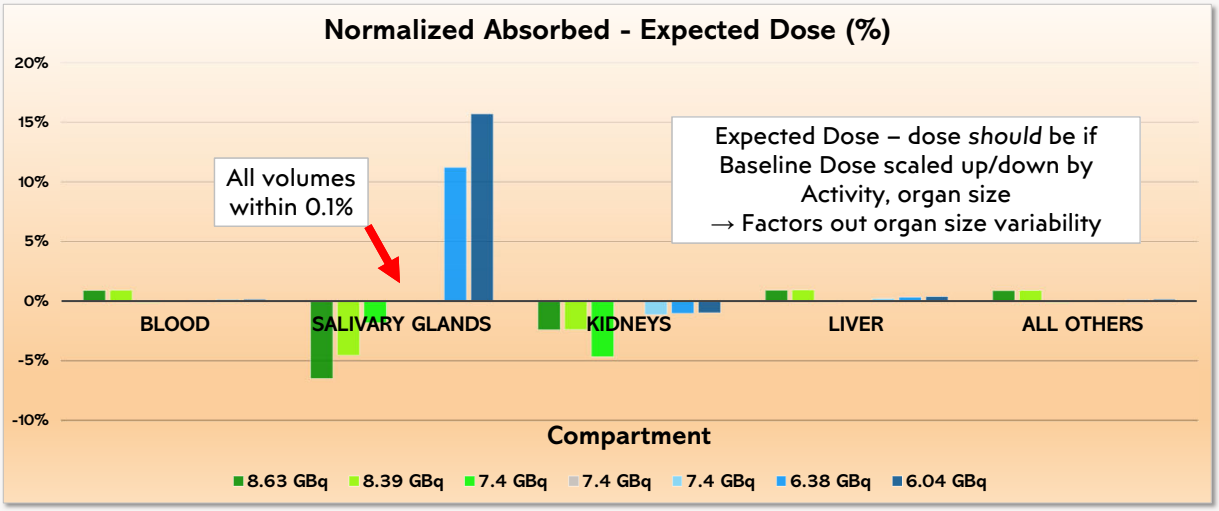
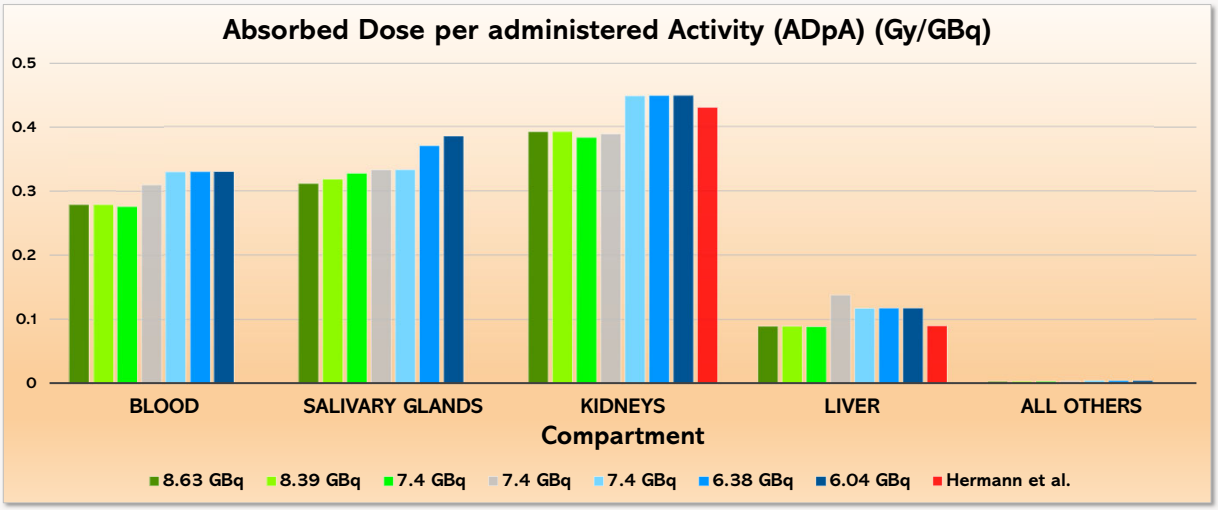
Results



26

Results



27

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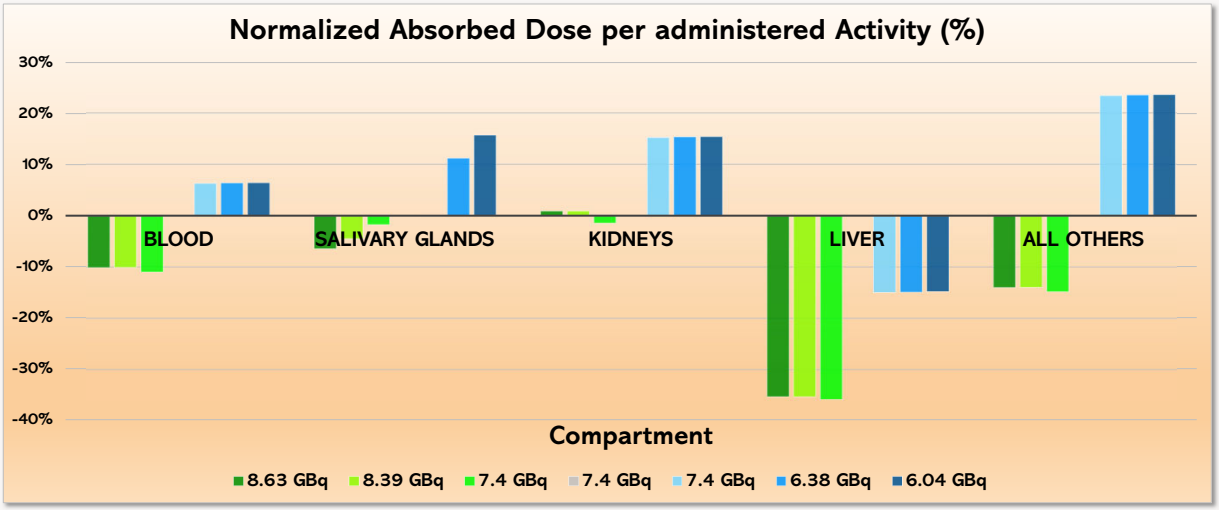
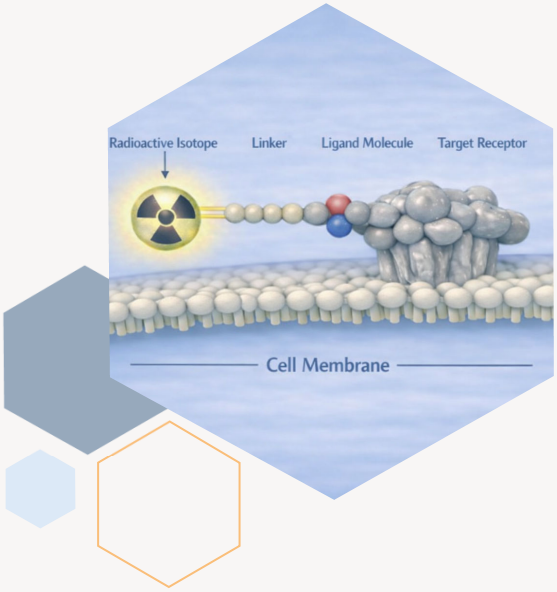


28

Summary

- Model Absorbed Doses and variability are consistent with published
- Absorbed Doses generally follow administered activity, but ADpA shows:
  - higher Dose/Activity in 75.6 kg phantom
  - lower Dose/Activity in 108 kg phantom
- Patient Variability leads to Dose Variability, but possibly less concern for organ toxicity for larger sized phantom
- Limitations:
  - Only 3 phantoms
  - Tumor dose not included



29

Conclusions

PET and SPECT/CT imaging currently provide the most established methods for patient-specific dosimetry.

Even without imaging, applying some form of patient-specific dosimetry for Pluvicto seems appropriate

Modeling could be a viable approach to patient-specific dosimetry, even in the clinical setting

Weight-based dosing may reduce inter-patient organ dosimetric variability and warrants further investigation

30

Take Home Message

PBPK modeling reproduced published organ dosimetry trends

Fixed 7.4 GBq dosing produces variable Absorbed Doses

Patient size influences organ dosimetry

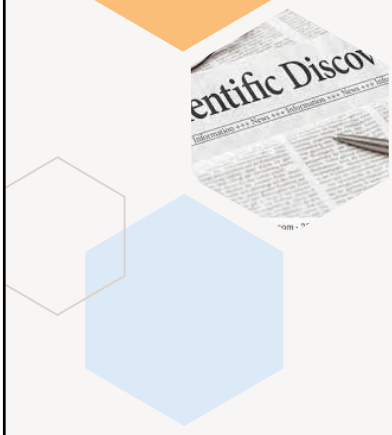
Modeling and Weight-based dosing may reduce inter-patient variability

Just like at Disney, despite the cost, for many the Magic is worth it and we can make sure it is only getting better

31

Questions?

32



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33

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34