



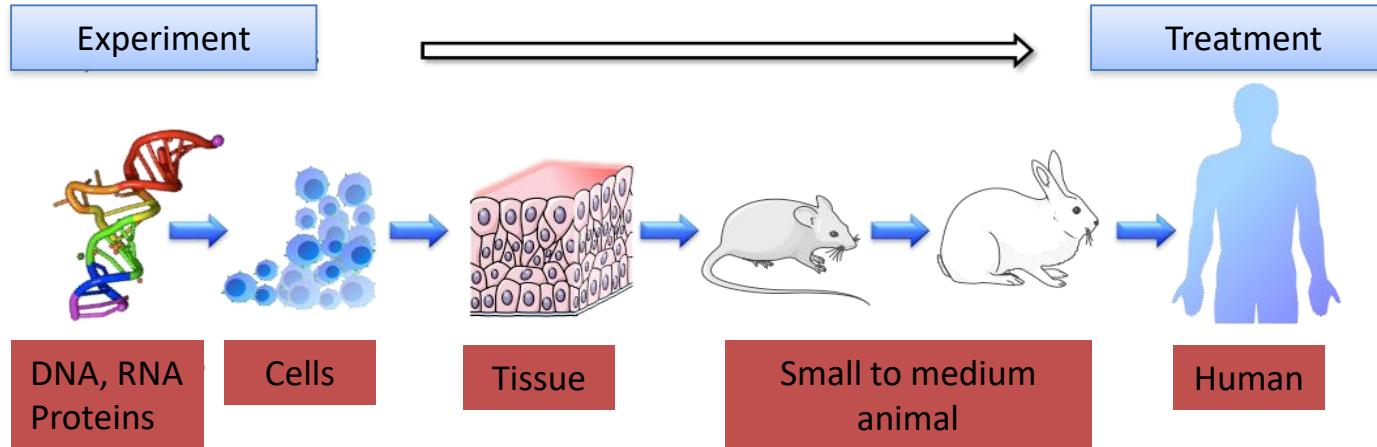
Small animal dosimetry: When, how?

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Small animal dosimetry?



When is dosimetry relevant for small animal experiments?

Designing a new radiopharmaceutical (diagnostic):

Assessing the *pharmacokinetics*

Derive / extrapolate human PK

Dosimetry on *human model* (not on the animal)

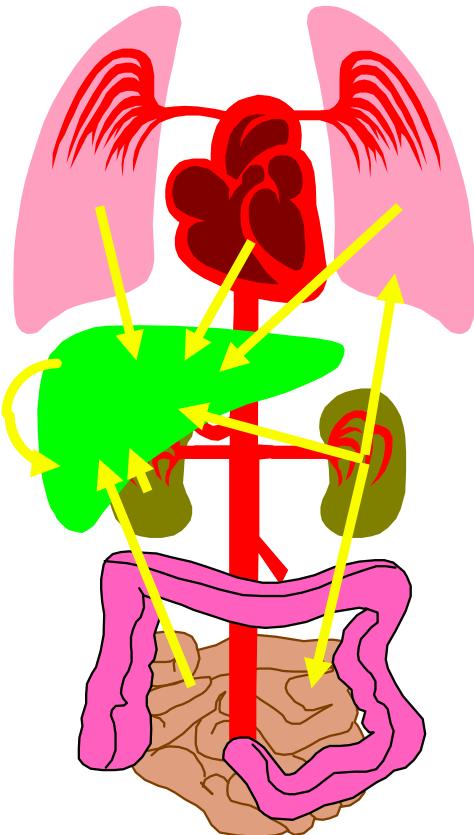
Experimental Molecular Radiotherapy

Animal dosimetry: to put in evidence/evaluate an effect

Efficacy/Toxicity

Radiopharmaceutical dosimetry: formalism

$$\bar{D}_{Target} = \sum_{Sources} \tilde{A}_{Source} \times S_{Target \leftarrow Source}$$

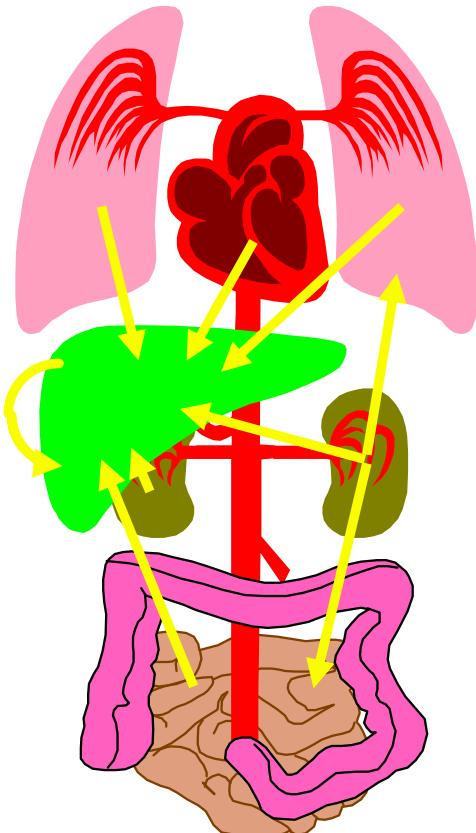


For each target of interest:

- For all sources
 - $A_{Source}(t)$ for all sources
 - Derive \tilde{A}_{Source} for all sources
- Get the «relevant» $S_{(Target \leftarrow Source)}$
- Sum all contributions to the irradiation of the target

A: New (diagnostic) radiopharmaceutical

$$\bar{D}_{Target} = \sum_{Sources} \tilde{A}_{Source} \times S_{Target \leftarrow Source}$$



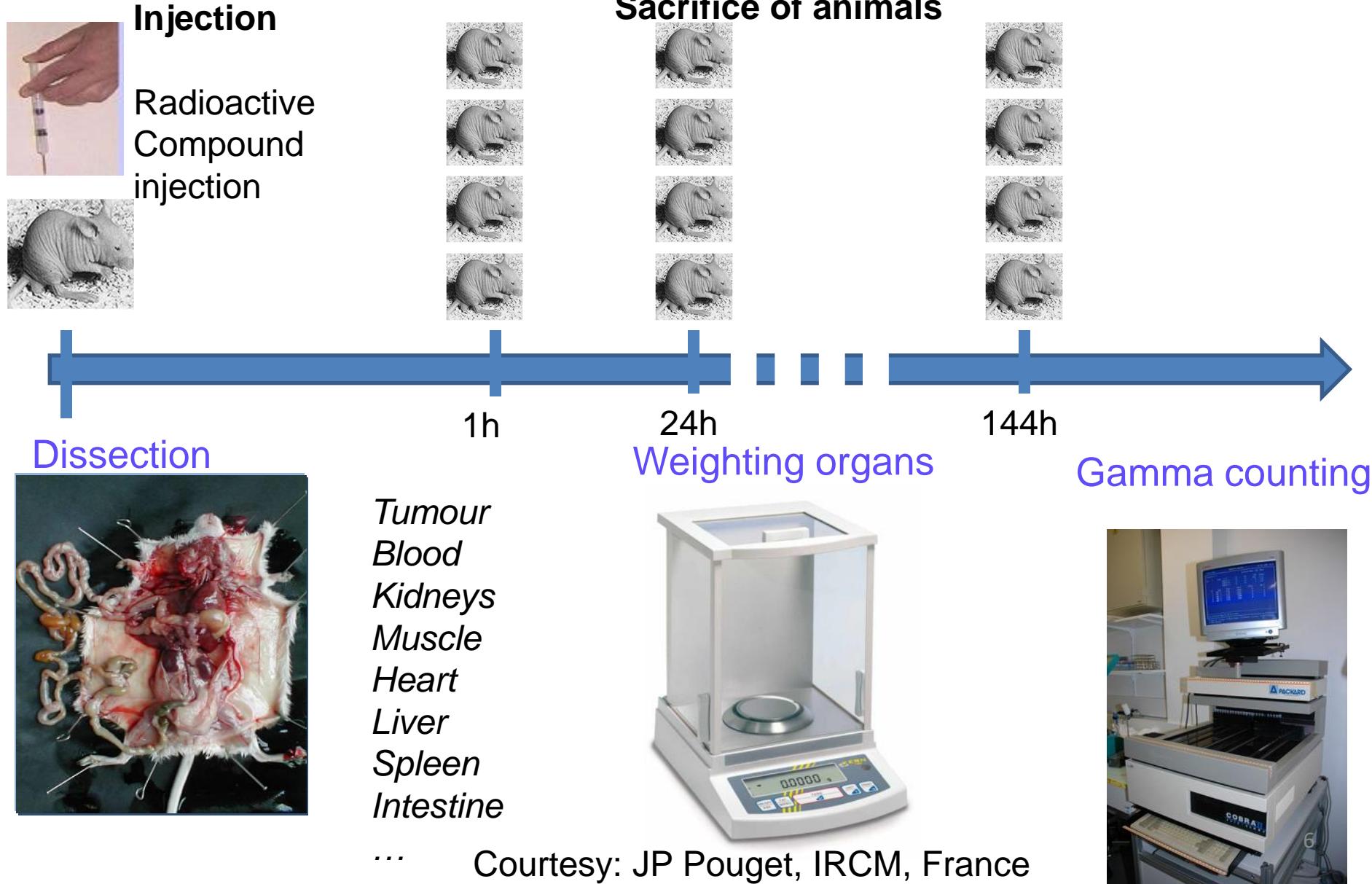
For each target of interest:

- For all sources
 - $A_{Source}(t)$ for all sources
 - Derive \tilde{A}_{Source} for all sources
- Extrapolate to human
- Get $S_{(Target \leftarrow Source)}$ from human dosimetric model
 - D for a « reference » human
 - Good enough for FDA/EMA

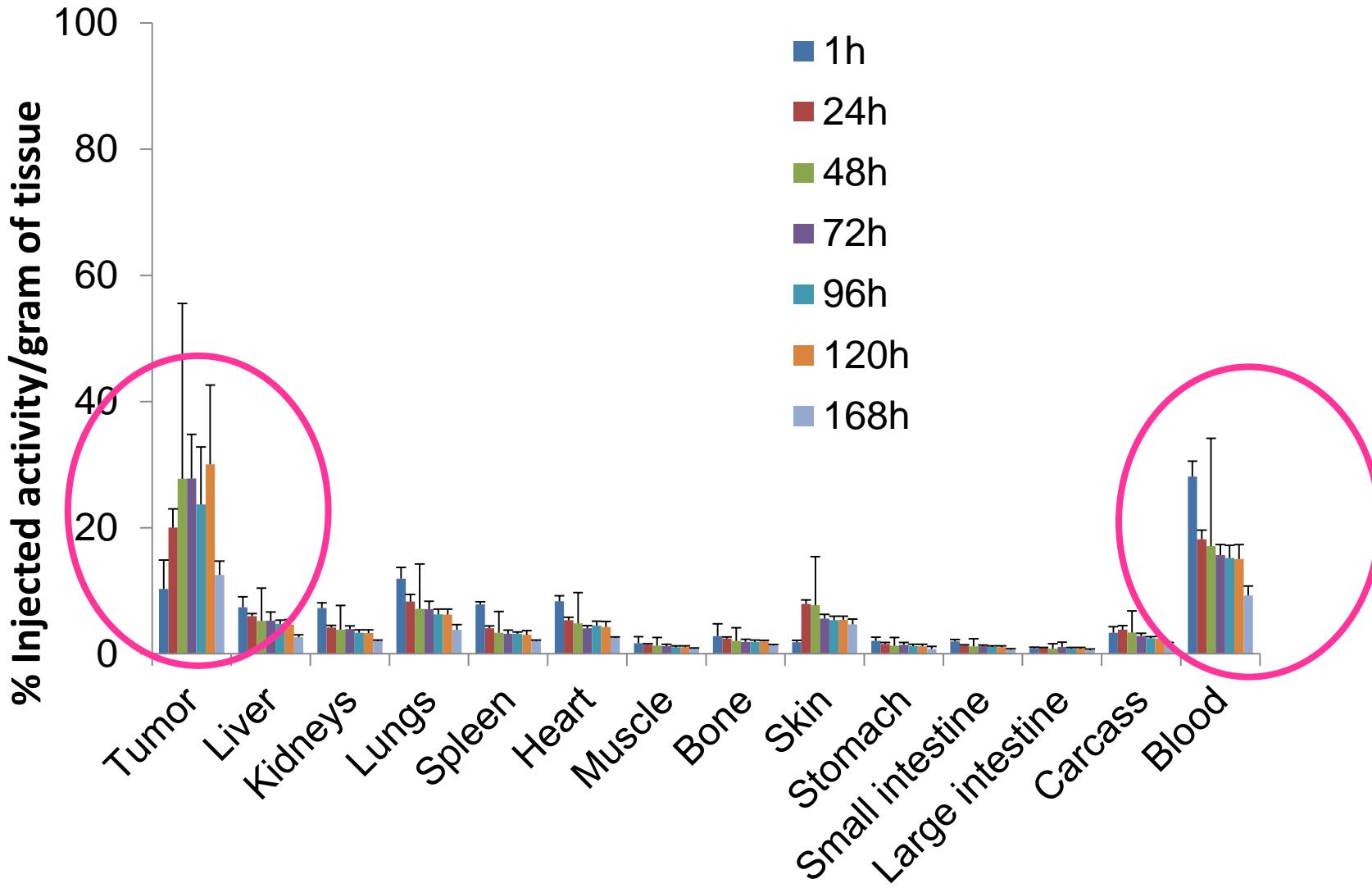
Cumulated activity $\tilde{A}_{\text{Source}}$

- Get $A_{\text{Source}}(t)$ (TAC), then integrate to get $\tilde{A}_{\text{Source}}$
- Applies to both new radiopharmaceutical design and experimental molecular radiotherapy
- Can be obtained by:
 - “cut-and-count” approaches
 - Quantitative imaging

“Cut-and-count“ approaches



Biodistribution ^{125}I -anti CEA MoAb (RIT)



Courtesy: JP Pouget, IRCM, France

Image-based pharmacokinetics

- Small animal imaging devices



NanoSPECT/CT; Bioscan



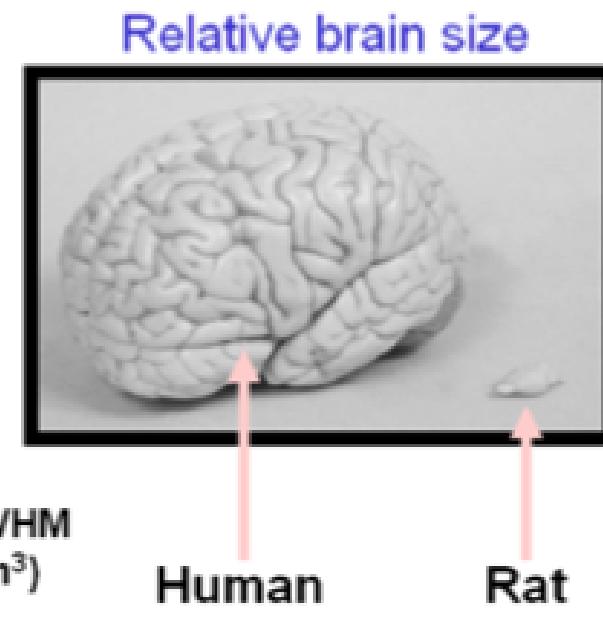
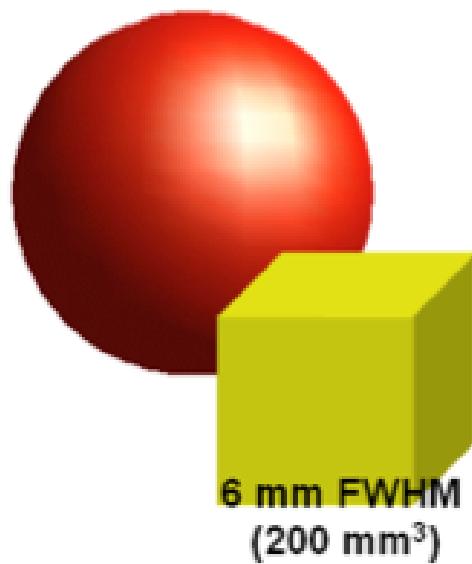
Inveon Module TEP; Siemens

Preclinical to clinical imaging

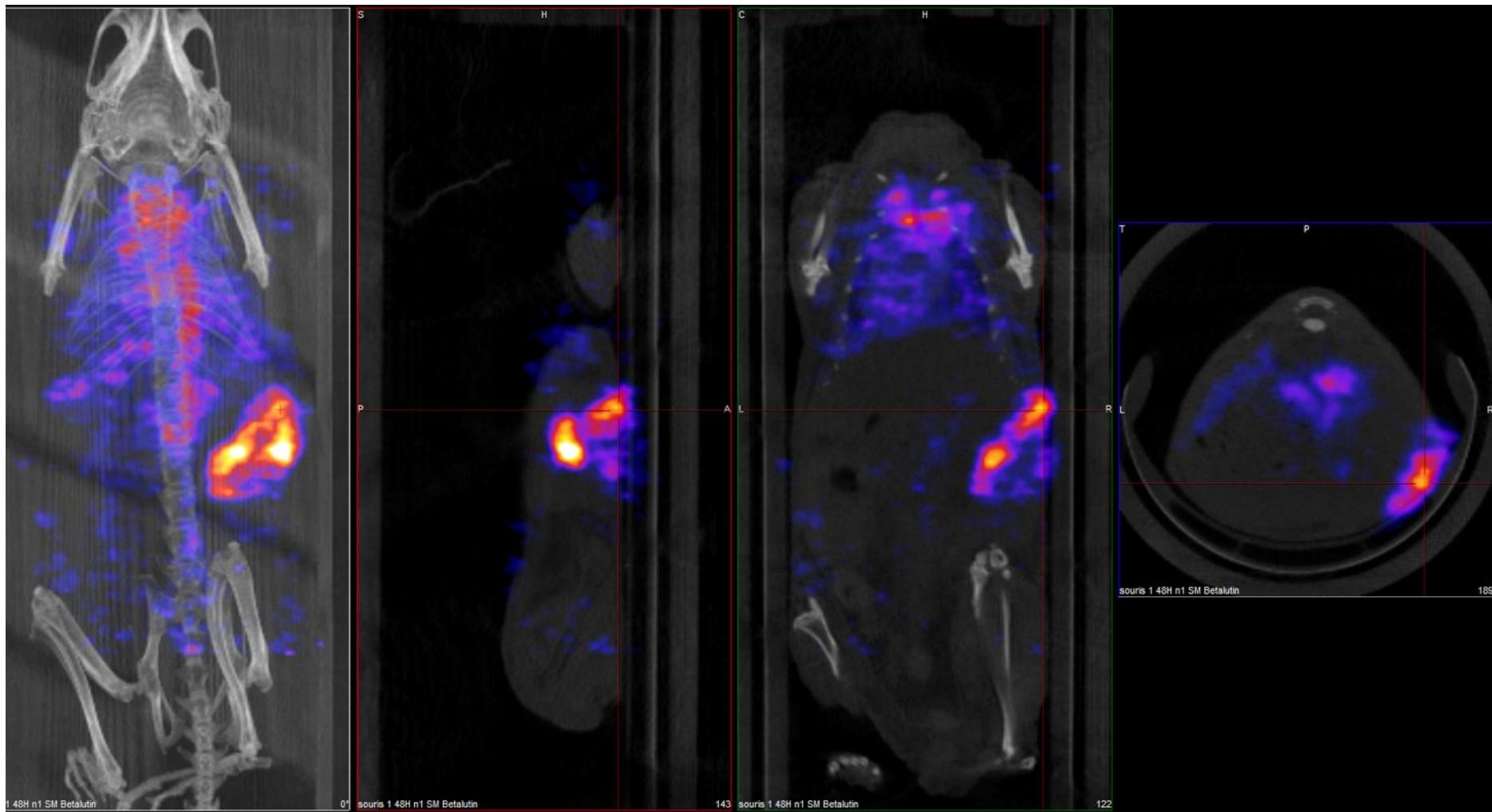
Human body: ~70 kg
Heart mass: ~300 g
Aortic cannula Ø: ~30 mm
Brain cortex apex – temporal lobe: ~105 mm

Rat body: ~200 g
Heart mass: ~1 g
Aortic cannula Ø: 1.5 - 2.2 mm
Brain cortex apex – temporal lobe: ~10 mm

Mouse body: ~20 g
Heart mass: ~0.1 g
Aortic cannula Ø: 0.9 - 1.3 mm
Brain cortex apex – temporal lobe: ~6 mm



Example



In vivo SPECT/CT of xenografted mice injected with 10 MBq of ^{177}Lu -labelled MoAB.
48 hours after injection

Image-based pharmacokinetics

- Longitudinal studies:
 - One batch of mice is imaged several times:
 - “mouse-specific” TAC
- Image quantification?
- Image registration and segmentation?
 - How to match images acquired at \neq time-points
 - Use CT but CT-induced irradiation?
 - Ex: ^{18}FDG – INVEON (Siemens microPET/CT) – $A_0 = 10 \text{ MBq}$
 - 100 mGy (whole-body)/FDG
 - 160 mGy (whole-body)/ μCT
 - (Hindorf *et al.* 2010 EJNMMI 37(Suppl 2) S274)

Quantitative imaging for ^{177}Lu preclinical imaging

Study	Administered activity of ^{177}Lu	Type of SPECT/CT - pinhole diameter	Acquisition protocol
Hijnen et al 2012	40 MBq for SPECT	nanoSPECT/CT bioscan - 1.0 mm	not described
Müller et al 2013	35 MBq for SPECT 20 MBq for therapy 2-3 MBq for biodistribution	nanoSPECT/CT bioscan - 1.0 mm	1, 4, 24, 72h 40-70 s /proj Scan time 30-60 min
Liu et al 2014	37 MBq for SPECT 14.8 MBq for therapy 0.37 MBq for biodistribution	nanoSPECT/CT bioscan - 1.4 mm	50 kCnts/proj 24 projections
Schoffelen et al 2012	90 MBq for SPECT 60 MBq for therapy	USPECTII/CT 1.0 mm	Scan time 60 min

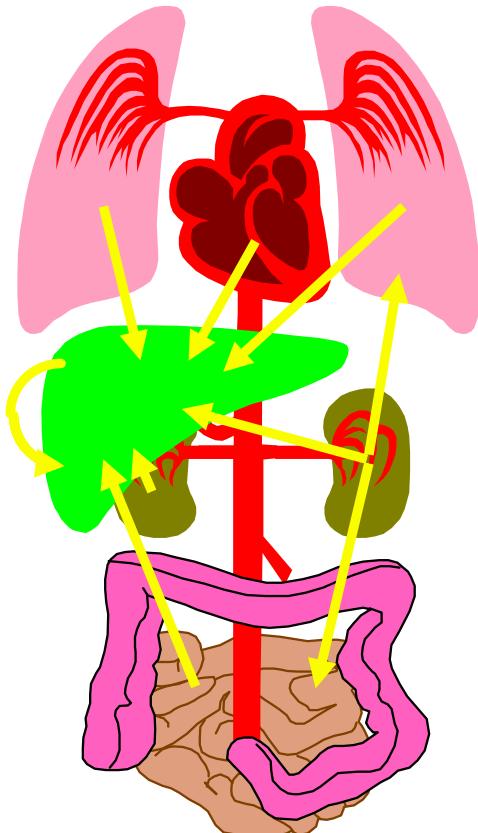
- Large variations in injected activities
- Imaging activity > to therapeutic activity?
- Quantification? (black box...)

Activity determination & PK assessment

- Image-based and “Cut-and-count” complement each other but do not always compare!
- Need for guidance documents
- Need to estimate uncertainties

A: New (diagnostic) radiopharmaceutical

$$\bar{D}_{Target} = \sum_{Sources} \tilde{A}_{Source} \times S_{Target \leftarrow Source}$$



For each target of interest:

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 - $A_{Source}(t)$ for all sources
 - Derive \tilde{A}_{Source} for all sources
- **Extrapolate to human**
- Get $S_{(Target \leftarrow Source)}$ from human dosimetric model
 - D for a « reference » human
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Allometry...

- Caveat!: %IA/g
 - 100% of the radioactivity in a 25g mouse:
4%IA/g
 - 100% of the radioactivity in a 70kg man:
1.4%IA/kg!

Preclinical Pharmacokinetics and Biodistribution Studies of ⁸⁹Zr-Labeled Pembrolizumab

Christopher G. England^{*1}, Emily B. Ehlerding^{*1}, Reinier Hernandez¹, Brian T. Rekoske², Stephen A. Graves¹, Haiyan Sun³, Glenn Liu^{2,4}, Douglas G. McNeel^{2,4}, Todd E. Barnhart¹, and Weibo Cai^{1,3,4}

J Nucl Med 2017; 58:162–168

DOI: 10.2967/jnumed.116.177857

Radiation Dosimetry Extrapolation to Humans

Dosimetry analysis was performed using OLINDA/EXM software (13). Estimated human dosimetry was calculated on the basis of average %ID/g values from the serial PET scans on both mice and rats, which were converted to %ID in humans. It was assumed that the biodistribution in adult humans was the same as in the animal models, and a monoexponential model was used for the time–activity curves. OLINDA provides effective dose outputs; thus, weighting factors from International Commission on Radiological Protection Publication 103 were used to convert to absorbed dose in each organ (14).

Biodistribution, Pharmacokinetics, and Dosimetry of ^{177}Lu -, ^{90}Y -, and ^{111}In -Labeled Somatostatin Receptor Antagonist OPS201 in Comparison to the Agonist ^{177}Lu -DOTATATE: The Mass Effect

Guillaume P. Nicolas^{1,2}, Rosalba Mansi³, Lisa McDougall^{1,3}, Jens Kaufmann⁴, Hakim Bouterfa⁴, Damian Wild^{1,2}, and Melpomeni Fani^{1,3}

J Nucl Med 2017; 58:1435–1441

Mouse biodistribution data were used to generate time–activity curves for each radiotracer. Because of the absence of a specific radioactivity accumulation in bones and red marrow, a linear relationship between the blood and the red marrow residence times was assumed for estimating the red marrow radiation dose (18). The proportionality factor was the ratio between the red marrow mass and the blood mass in humans. OLINDA/EXM 1.0 was used to integrate the fitted time–activity curves and to estimate the organ and effective doses using the whole-body adult female model. For all calculations, the assumption was made that the mouse biodistribution, determined as the %IA/organ, was the same as the human biodistribution.

Brian J. McParland

Nuclear Medicine Radiation Dosimetry



Advanced
Theoretical Principles

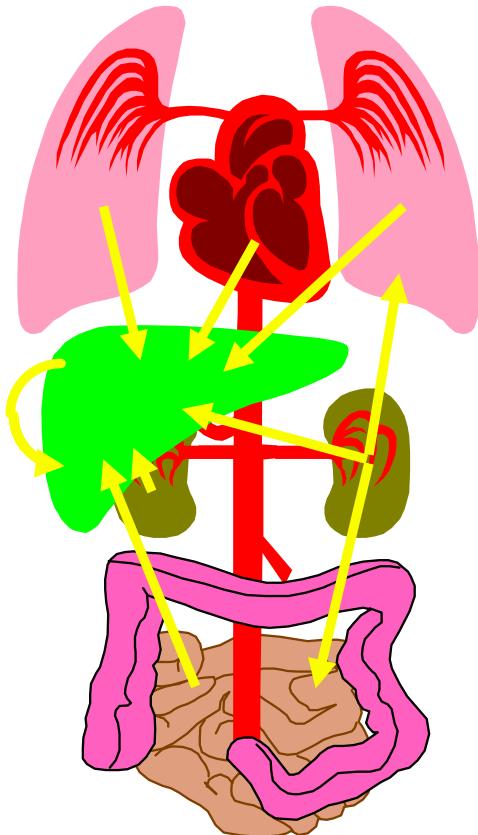
$$\tilde{A}_{Organ,Human} = \left(\frac{m_{Animal}}{m_{Human}} \right)_{WB} * \left(\frac{m_{Human}}{m_{Animal}} \right)_{Org} * \tilde{A}_{Organ,Animal}$$

Allometry...

- Allometry: depends on the radiopharmaceutical
- No consensus
- Most often not well documented

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Computing models

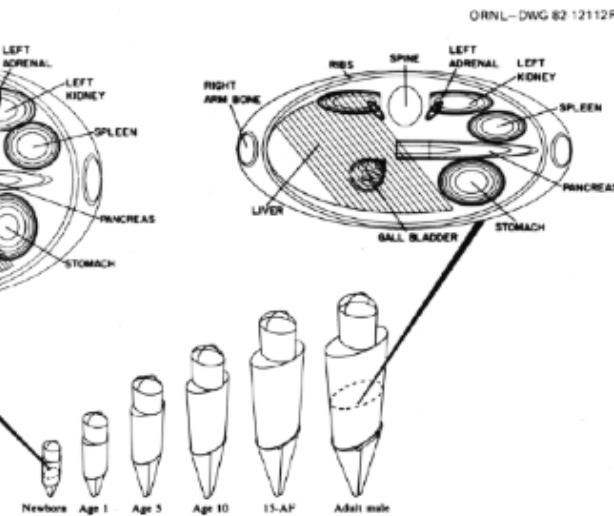
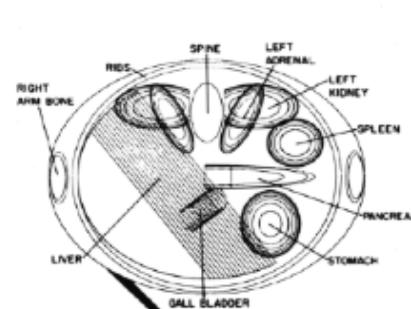
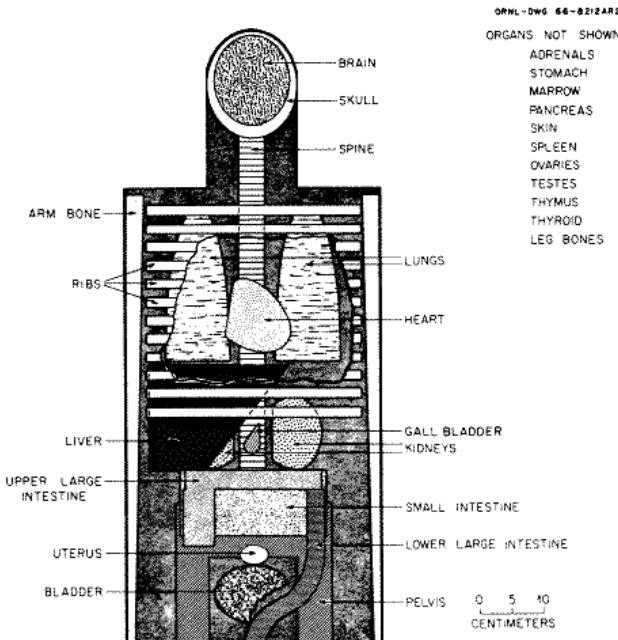


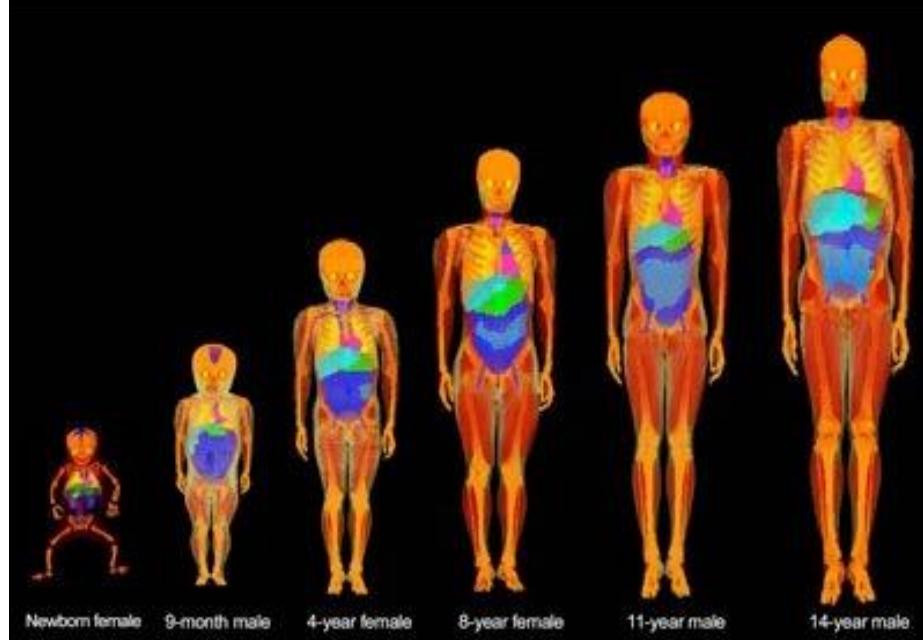
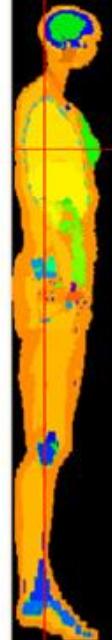
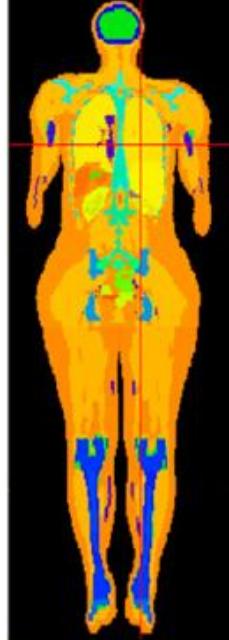
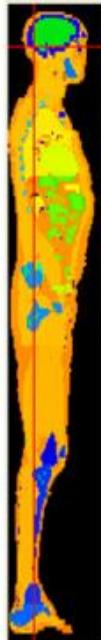
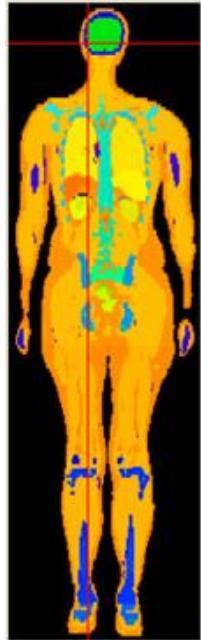
Fig. A-3. Anterior view of the principal organs in the head and trunk of the adult phantom developed by Snyder et al. (1974). Although the heart and head have been modified in this report, this schematic illustrates the simplicity of the geometries of the organs.

Snyder 1975

Cristy & Eckerman
1987



Computing models



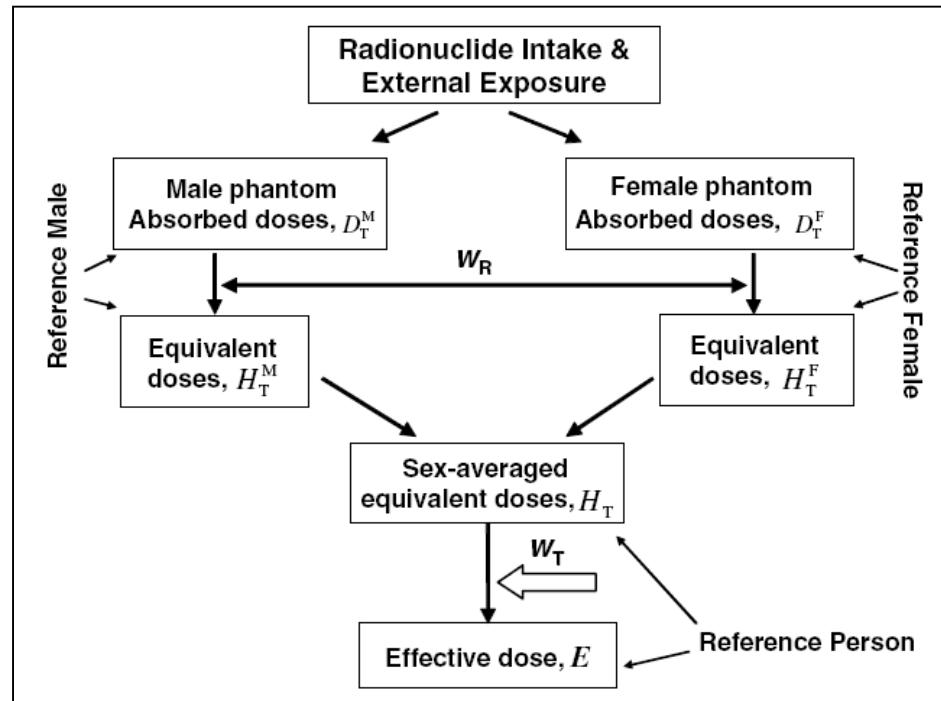
Reference Adults
ICRP 110

Paediatric series
ICRP 143



ICRP Evolution

- Reference report ICRP 103
 - New computing models (ICRP 110 + 143)
 - New calculation scheme
 - New weighting factors
- Transition phase!
(ex: ICRP 128)



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Dosimetric data for ICRP 103

IDAC-Dose2.1

a new internal dosimetry
program for diagnostic
nuclear medicine based on
the new ICRP adult reference
SAF values

Download IDAC-Dose2.1

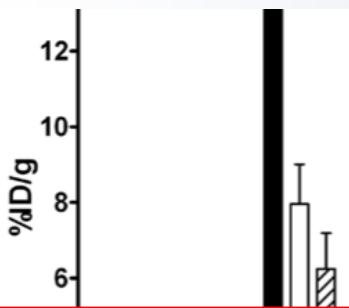
- Only for reference adults!
- <http://www.idac-dose.org>

Andersson M., Johansson L., Eckerman K. and Mattsson S. IDAC-Dose 2.1, an internal dosimetry program for diagnostic nuclear medicine based on the ICRP adult reference voxel phantoms. EJNMMI Research 2017

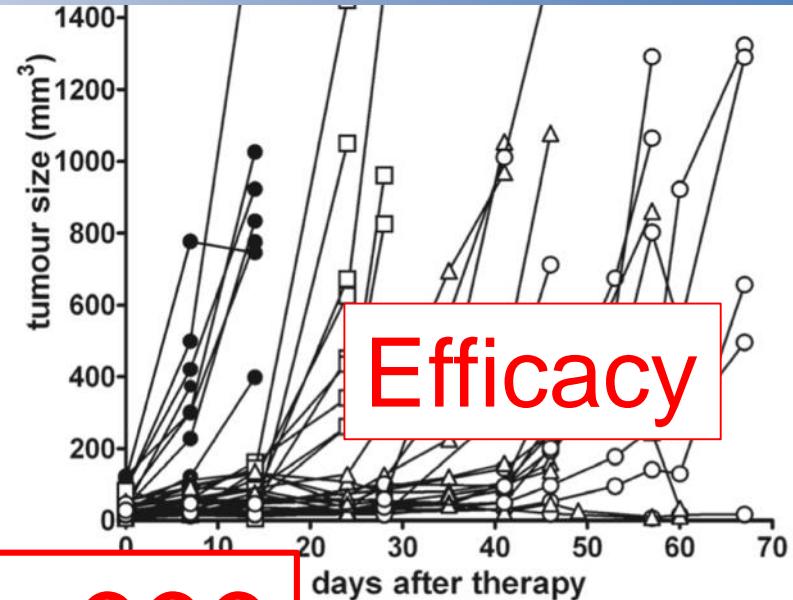
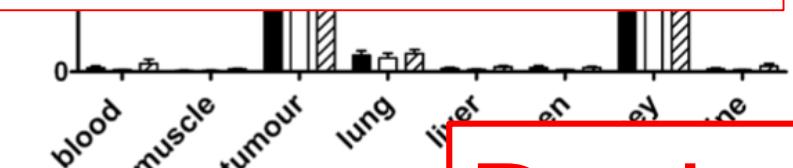
Computing models & dosimetry...

- “Some” available tools, but limited documentation
- Need for guidance documents on how to implement ICRP 103 recommendations in practice...

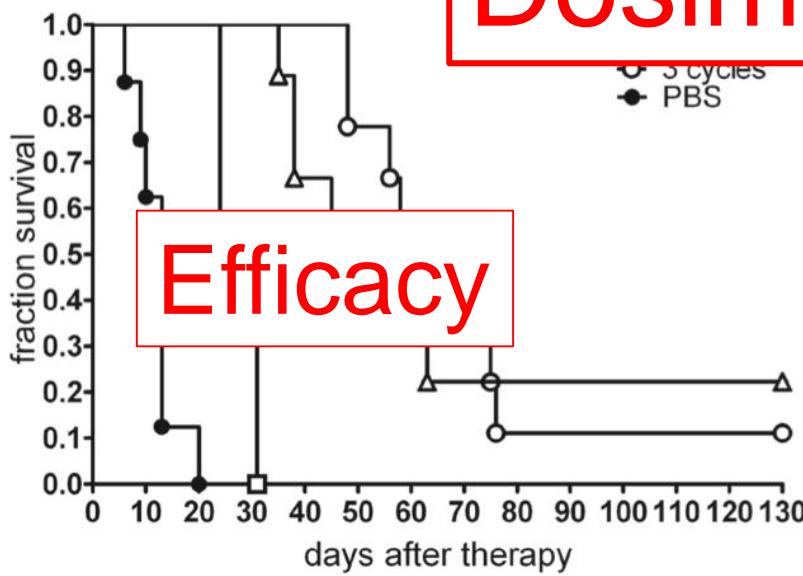
B: Experimental Molecular Radiotherapy



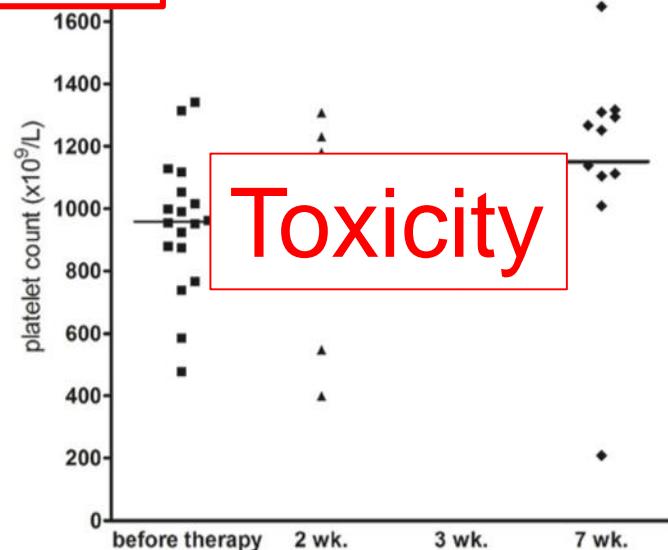
Pharmacokinetics



Efficacy



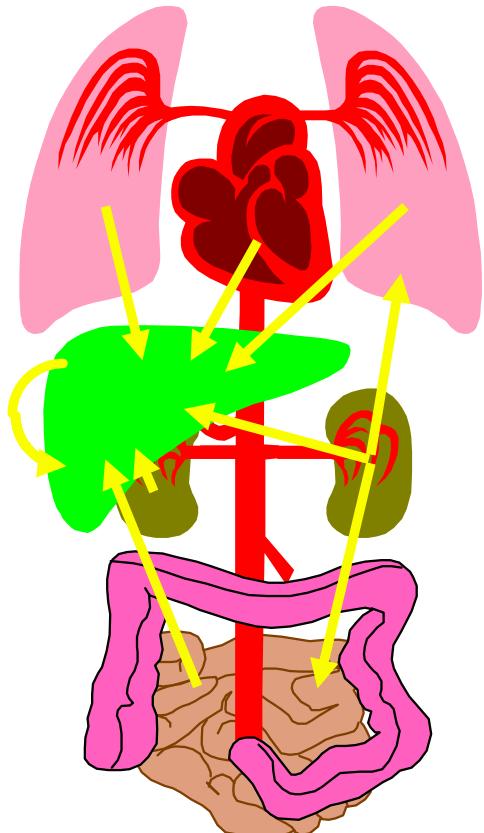
Efficacy



Toxicity

B: Experimental Molecular Radiotherapy

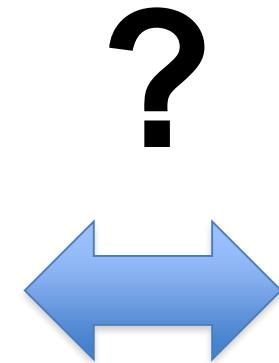
$$\bar{D}_{Target} = \sum_{Sources} \tilde{A}_{Source} \times S_{Target \leftarrow Source}$$



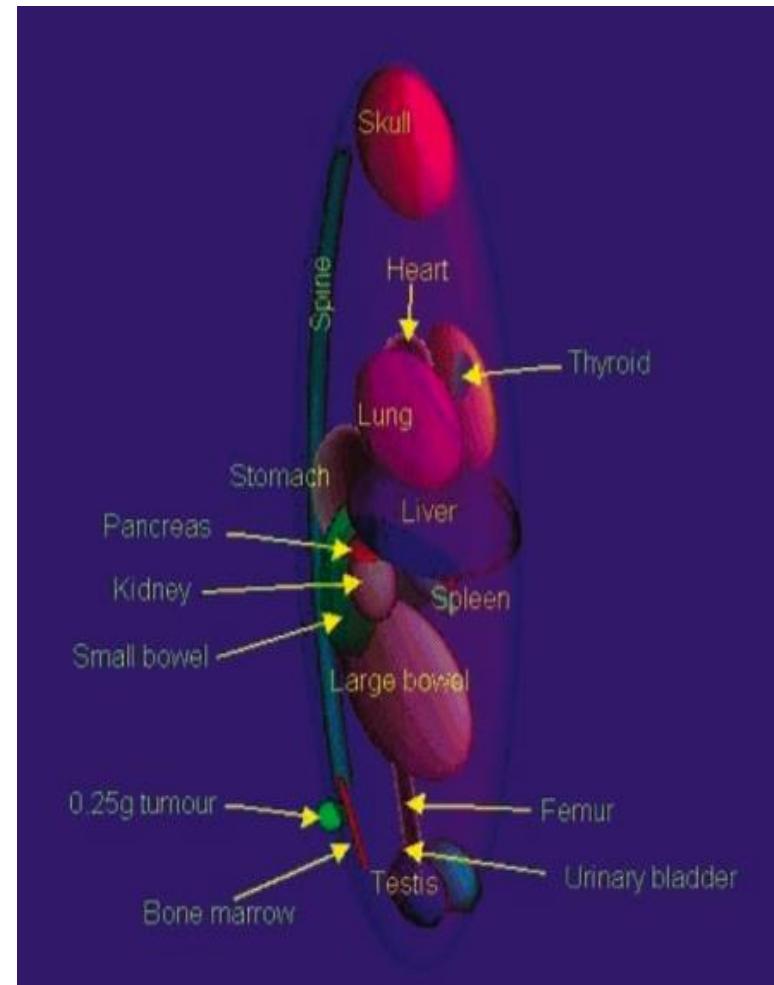
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 - Derive \tilde{A}_{Source} for all sources
- Get $S_{(Target \leftarrow Source)}$ from small animal dosimetric model, or compute D specifically

Specific vs. Model



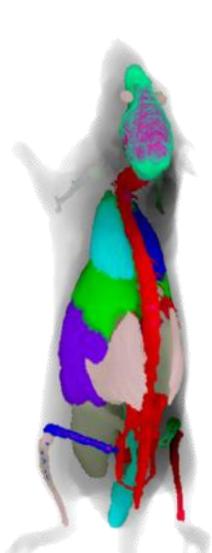
?



If \bar{A} averaged (group of mice),
“mouse-specific” dosimetry?
-> use a dosimetric model

Konijnenberg *et al.*
J Nucl Med. 2004;45:1260–1269

Dosimetric voxel-based models

Dosimetric Models				
Stabin 2006	<i>Stabin et al 2006</i>	<i>Larsson 2007</i>	<i>Bitar et al 2007</i>	<i>Boutaleb et al 2009</i>
Atlas	<i>Stabin et al 2006</i>	<i>Segars 2003</i>	<i>Bitar et al 2007</i>	<i>Dogdas et al 2007</i>
Souche	<i>"Transgenic "</i>	<i>C57BL/6</i>	<i>Swiss Nude</i>	<i>Swiss Nude</i>
Mass	<i>27-g</i>	<i>33-g</i>	<i>30-g</i>	<i>28-g</i>
Matrix	<i>256x256x256</i>	<i>128x432x128</i>	<i>220x450x111</i>	<i>190x496x104</i>
Voxel (mm)	<i>0.2x0.2x0.2</i>	<i>0.25x0.25x0.25</i>	<i>0.220x0.220x0.2</i>	<i>0.2x0.2x0.2</i>

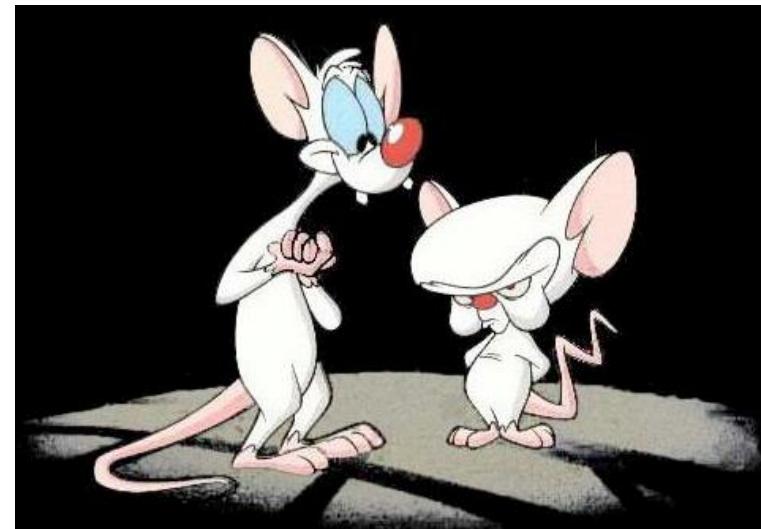
Comparison of 2 models (^{131}I)

Targets	Masses	Source organs (\$ in Gy.Bq $^{-1} \cdot \text{s}^{-1}$)		
		Liver	Spleen	Lungs
Liver	Female 30g	$1.60 \cdot 10^{-11}$		
	Male 28g	$1.21 \cdot 10^{-11}$		$1.53 \cdot 10^{-12}$
	Difference			$9.96 \cdot 10^{-13}$ -3.6 %
Kidneys	Female 20g			$4.95 \cdot 10^{-14}$
	Male 18g	$1.21 \cdot 10^{-11}$	$1.21 \cdot 10^{-11}$	$3.98 \cdot 10^{-14}$ 57.8 %
	Difference			24.4 %
Lungs	Female 15g	$1.55 \cdot 10^{-12}$	$5.05 \cdot 10^{-14}$	$1.59 \cdot 10^{-10}$
	Male 13g	$1.01 \cdot 10^{-12}$	$4.01 \cdot 10^{-14}$	$1.57 \cdot 10^{-10}$
	Difference	53.5 %	25.9 %	1.27 %

Different results!
No reference!

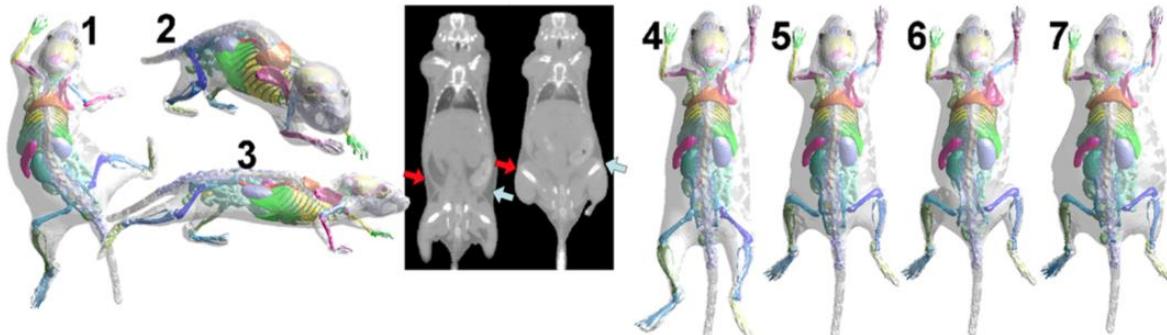
Mouse dosimetric models?

- Different mice strain, age, sex, weight...
- Different S factors
- The mass adjustment does not work for high energy emitters such as ^{90}Y ...

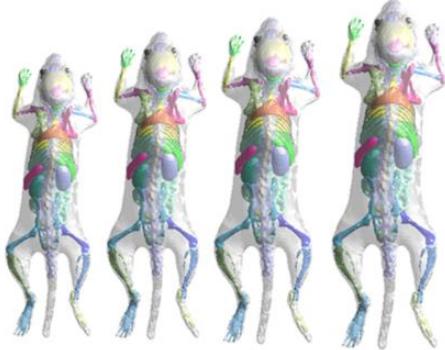


Model database?

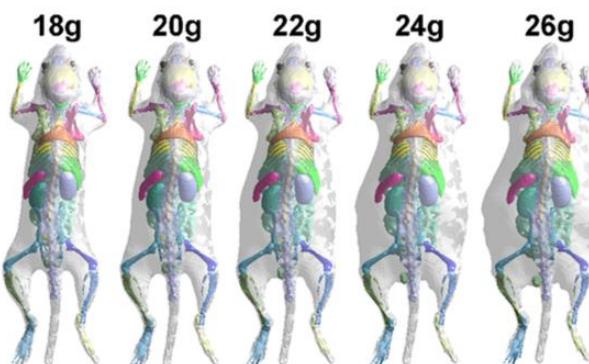
a



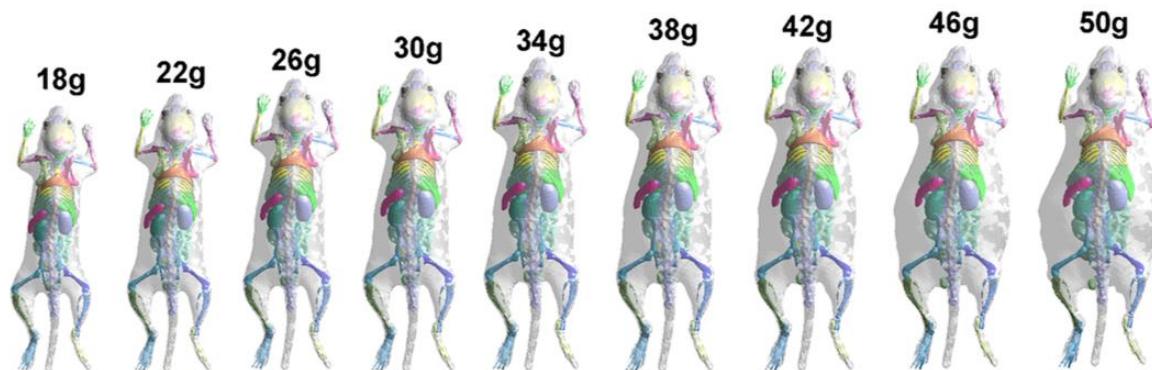
b



c



d



Wang *et al.*
Mol Imaging Biol 2014

Specific dosimetry

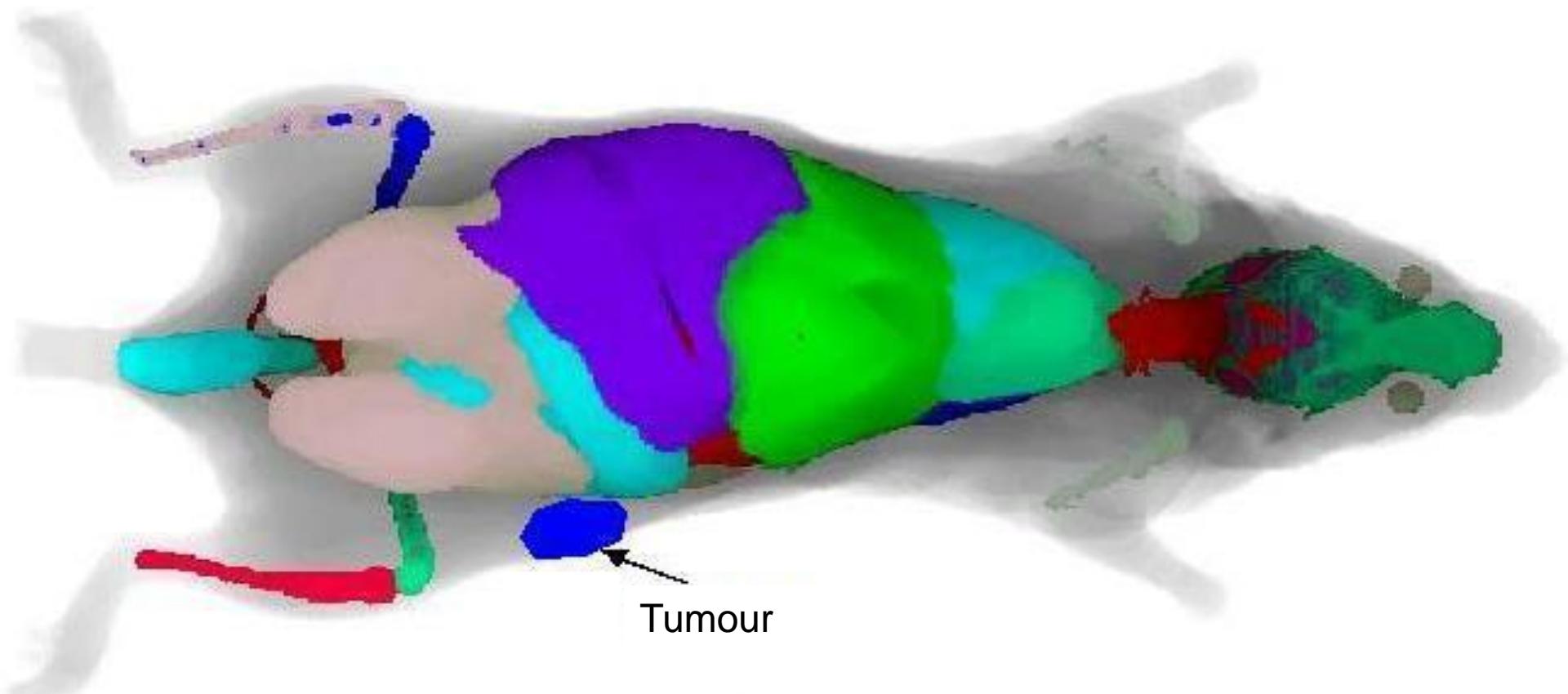
Gestin et al. J. Nucl. Med. 42; 146-, 2001



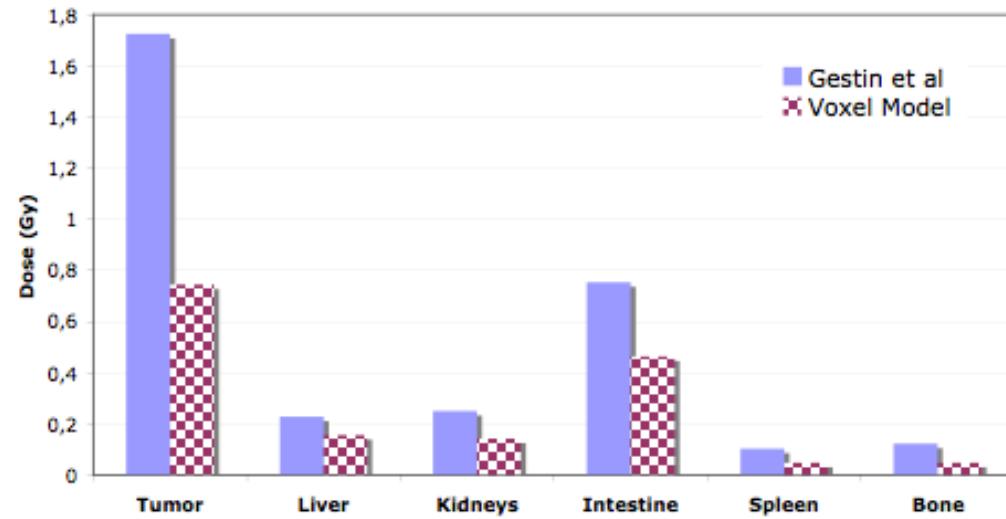
^{188}Re and ^{131}I :
non-penetrating radiations

$$\overline{D}_{(h \leftarrow h)} = \frac{\tilde{A}_h \cdot \Delta}{m_h}$$

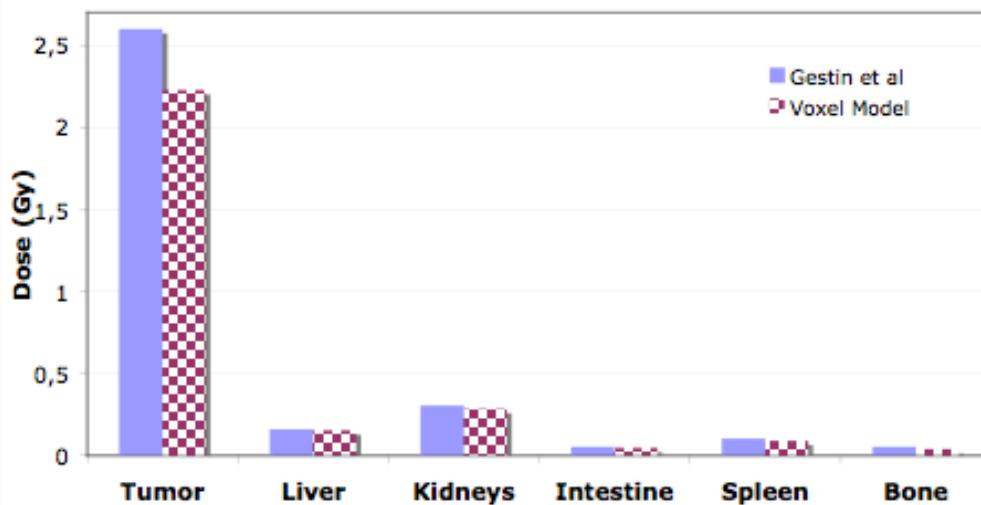
Adding a tumour



Results

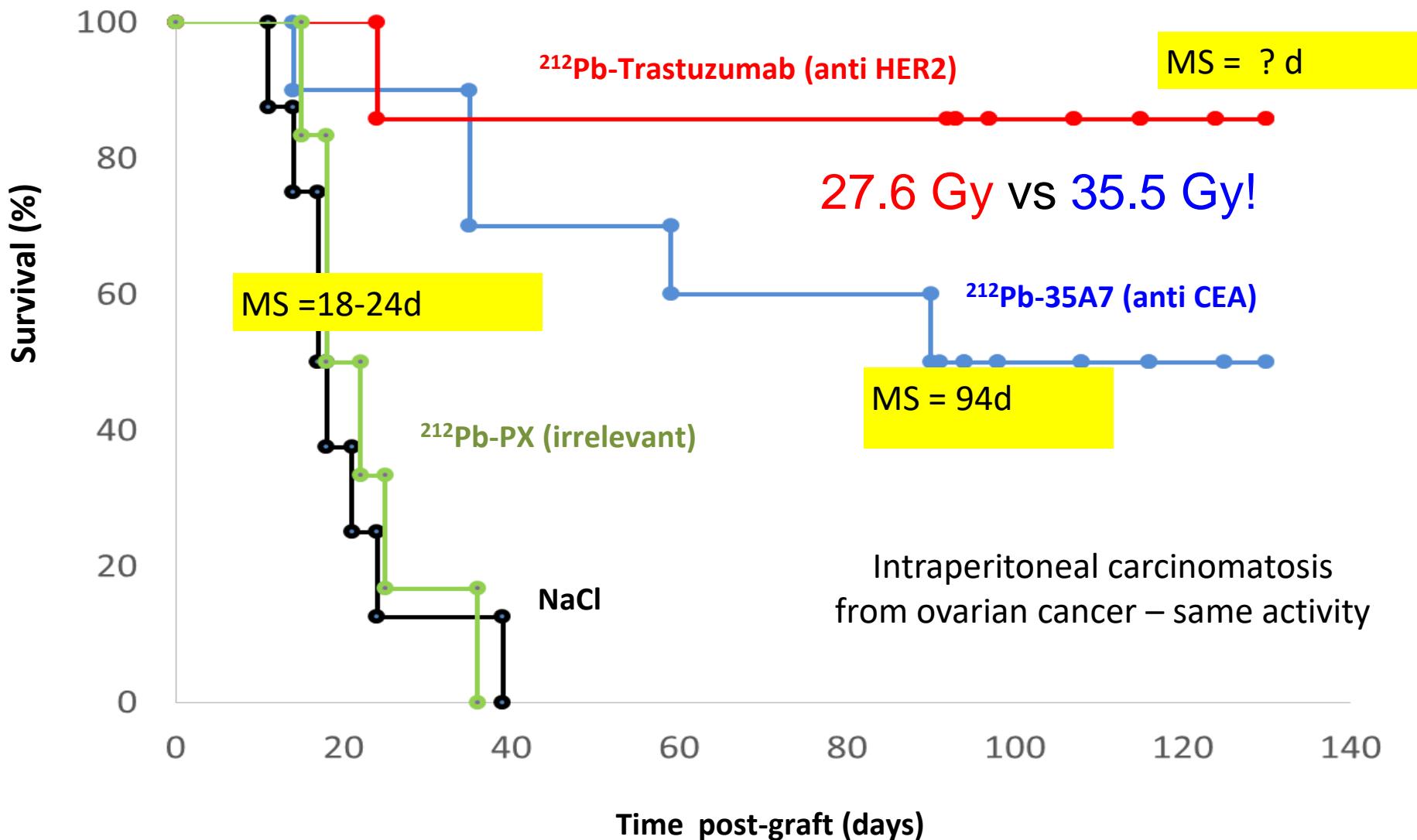


^{188}Re



^{131}I

Small-animal: Absorbed dose–effect relationship?



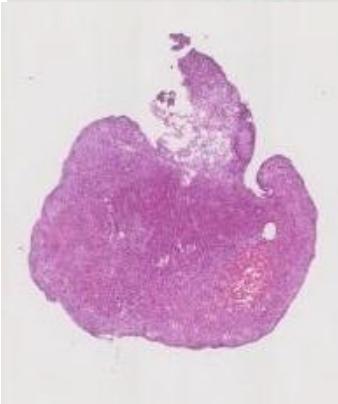
Small-animal: Absorbed dose–effect relationship?

^{212}Pb -anti HER2

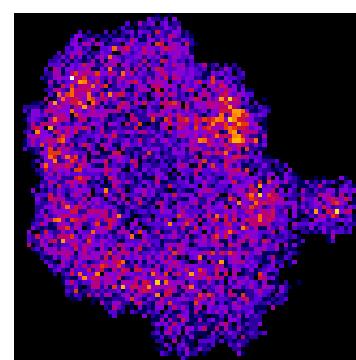
Immuno-histochemistry



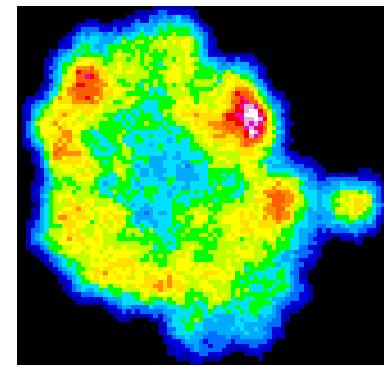
^{212}Pb -anti CEA



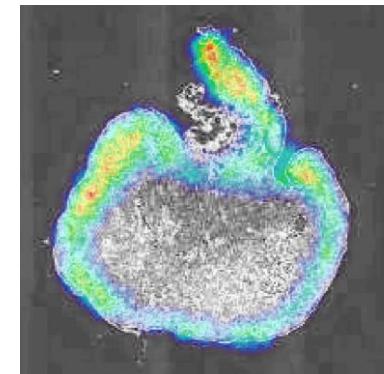
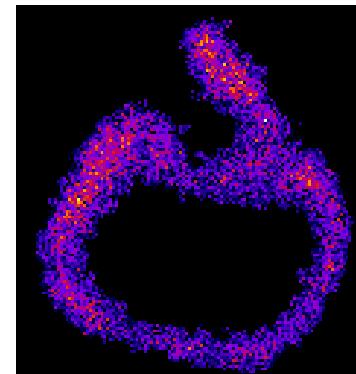
Digital autoradiography



Absorbed dose



G1



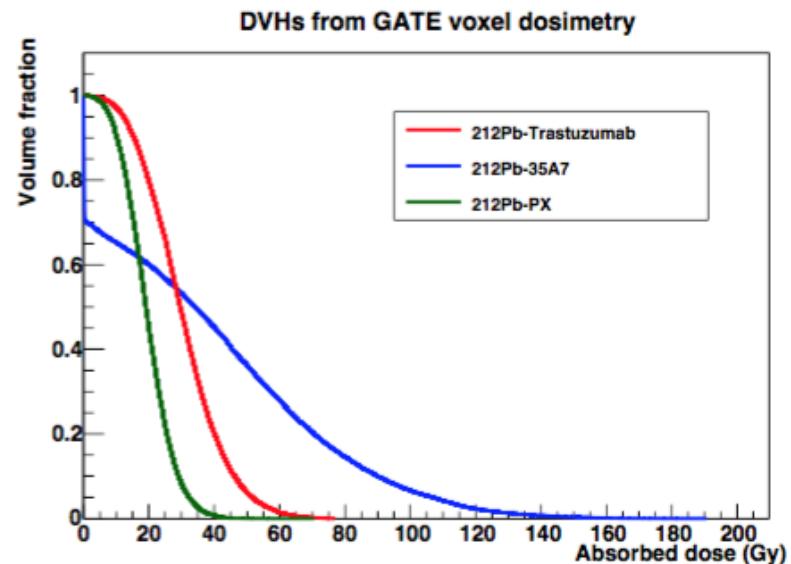
G2

Impact of tissue/pharmacokinetics heterogeneity?

Voxel dosimetry: results and conclusions

Average absorbed dose (Gy)

Group	Average dosimetry	Voxel dosimetry
Boudousq et al. 2013		This study
G1	27.6	30.5
G2	35.5	38.2
G3	-	19.4



- Average dosimetry still cannot explain survival
- Dosimetry carried out at the relevant scale allowed demonstrating an absorbed dose-effect correlation for ^{212}Pb -mAbs animal experiments.

Interesting example

Organ	Mouse (Gy/MBq)			Human (Gy/GBq)
	Self	Cross	Total	(n=13)
Liver	3.2	0.2	3.4	9.7
Spleen	2.0	2.4	4.4	
Kidneys	1.2	0.6	1.8	1.5
Red Marrow	0.5	1.1	1.6	0.6
Lungs				0.3
Whole Body				0.6
Tumours	4.6	0.5	5.1	26.7 (n=18)

- From “Radiopharmaceuticals” LE Williams CRC press 2011
- RIT ^{90}Y -anti-CEA antibody
- Mass ratio: ~2000-3000...

Small animal dosimetry...

- Doable!
 - Several models available
 - Specific dosimetry feasible too
 - Some absorbed dose effect relationship (ADER)
 - But Gy don't extrapolate from animal to human!
- No reference approach
- Need for some guidance document...

General conclusion: key points and recommendations

Preclinical (small animal) dosimetry

- **No reference methodology**
 - Difficult to compare results
- **Need for multidisciplinary education**
 - Small animal imaging ≠ clinical imaging: specific issues
 - Allometry...
 - Dosimetry calculations for mice and men...
 - Input for radiobiology
- **Case for guidelines?**
 - Preclinical dosimetry for drug development